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DEFINITIONS OF pH SCALES[1]

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I. INTRODUCTION

There is an increasing demand for accurate pH measurements in industry as well as in the research laboratory. Commercial pH meters, some of which are claimed to yield pH values reproducible to 0.005 pH unit, are found in nearly every laboratory where chemical analyses and tests are performed. These instruments almost universally utilize glass electrodes and calomel electrodes. They measure the acidity or alkalinity of the aqueous solution under examination with reference to a standard buffer solution with which the meter is calibrated from time to time.

Unfortunately, progress toward an accepted definition of pH has not kept pace with the development of devices for pH measurement, and a given solution may be assigned different pH values in different laboratories. Although adoption of different symbols has been urged (88, 98, 153), several scales, all masquerading under the name pH, are in common use. Many investigators are thinking and computing in terms of one definition and measuring a different quantity. This state of confusion results in part from the impossibility of determining exactly either $-\log m_H$ or $-\log \mathbf{a}_H$, where m_H and $\mathbf{a}_H$ are, respectively, the molality and the activity of hydrogen (hydronium) ion,[2] for a buffer solution of moderate concentration.

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[1] A paper based on this review was presented at the 110th Meeting of the American Chemical Society, which was held at Chicago, Illinois, September, 1946.

A large part of the present confusion would be removed if, by general agreement, a single scale of pH were adopted. It is the purpose of this paper to set forth the advantages and limitations of several possible units of acidity, in an effort to choose the most suitable scale. The assumptions that underlie the calculation of hydrogen-ion activity from the electromotive force of cells with and without liquid junction will be discussed.

II. THE SØRENSEN pH AND SCALES OF CONCENTRATION AND ACTIVITY

Sørensen (149) defined the pH value, which will be written pcH, as

$$\text{pcH} \equiv -\log c_H \tag{1}$$

where c is the molar concentration. We shall see presently that the pH value obtained by the operations and calculations specified by Sørensen is not, as he intended, a measure of hydrogen-ion concentration.

When the pH unit was first defined, it was believed that the partial molal free energy of transfer of hydrogen ion, ΔF, could be expressed exactly by the classical equation,

$$\Delta F = RT \ln (c_{H_1}/c_{H_2}) = -\mathbf{F}E \tag{2}$$

where $\mathbf{F}$ is the faraday, R and T are, respectively, the gas constant and the absolute temperature, and E is the electromotive force of the concentration cell,

$$\begin{array}{lllll} H_2; & \text{solution} & \text{KCl,} & \text{KCl,} & Hg_2Cl_2\,;Hg\text{—} \\ & 1 & 3.5\ N & 0.1\ N & \end{array}$$

$$\begin{array}{lllll} Hg;Hg_2Cl_2, & \text{KCl} & \text{KCl} & \text{solution};H_2 & \text{Cell I} \\ & 0.1\ N & 3.5\ N & 2 & \end{array}$$

corrected for the liquid-junction potentials between 3.5 *N* potassium chloride and solutions 1 and 2. The liquid junctions in cell I are indicated by vertical lines. Sørensen (150, 151, 152) based his pH scale on E.M.F. measurements of cell I with the use of solutions of hydrochloric acid and mixtures of hydrochloric acid and sodium or potassium chlorides as solution 1. It was assumed that the values of c_{H_1} in these reference solutions were given by αM, where M was the molar concentration of hydrochloric acid, and α, the classical degree of dissociation of hydrochloric acid, was computed from measurements of electrolytic conductance. For convenience, this standard was expressed in terms of E^0, the electromotive force of the cell,

$$\begin{array}{lllll} H_2;\text{solution} & \text{KCl,} & \text{KCl,} & Hg_2Cl_2;Hg & \text{Cell II} \\ \quad 1 & 3.5\,N\text{ or} & 0.1\,N & & \\ & \text{saturated} & & & \end{array}$$

---

[2] The term "hydrogen ion" will hereafter refer to the hydrated proton. The term "pH measurement" will refer to measurements of acidity in general, without indicating the scale used.

when the hydrogen-ion concentration in solution 1 was 1 normal. The liquid-junction potential is not included in the value of E^0. Cell II could then be used, it was supposed, to compute the pH values of other solutions by the following equation,

$$E = E^0 - \frac{RT}{\mathrm{F}} \ln c_{\mathrm{H}} \tag{3}$$

in which E is again corrected for the difference of potential across the liquid junction.

Conversion of equation 3 to common logarithms and substitution of Sørensen's definition of pH and his value of E^0 for cell II at 25°C. (149, 152, 153) gives

$$\mathrm{psH} \equiv \frac{E - 0.3376}{0.05914} \tag{4}$$

The pH values computed by this equation will be designated psH.

The advent of modern chemical thermodynamics and new concepts of electrolytic solutions clarified the meaning of psH in some degree but did not offer a unique solution to the problem of measuring acidity. Modified definitions of pH have appeared but have failed to supplant the older ones. The activity has superseded the concentration in equations for free energy, and it is now realized that neither the activity nor the concentration of hydrogen ion can be derived from αM for a solution of a strong acid, yet Sørensen's pH scale continues to be commonly used. It is evident that the psH value is neither $-\log c_{\mathrm{H}}$ nor $-\log \mathbf{a}_{\mathrm{H}}$.

From the form of the newer free-energy equation, it was reasonable to define a new pH value (153),

$$\mathrm{paH} \equiv -\log \mathbf{a}_{\mathrm{H}} \tag{5}$$

where $\mathbf{a}_{\mathrm{H}}$ is $f_{\mathrm{H}}c_{\mathrm{H}}$ or $f_{\mathrm{H}}m_{\mathrm{H}}$ and f is the activity coefficient corresponding to the scale of concentration.[3] The psH value is nearly equal to $-\log 1.1\mathbf{a}_{\mathrm{H}}$ (84, 90, 153). Hence

$$\mathrm{paH} = \mathrm{psH} + 0.04 \tag{6}$$

Equation 6 is very satisfactory from a practical viewpoint as a formula for converting to the activity basis the extensive tables of Sørensen values given by Clark (25), Britton (19), and others.

Adoption of equation 5 as the definition of an acidity function obviously will not, of itself, fix a scale of paH. If cell II or a similar one is used, the standardiza-

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[3] The standard state of unit activity coefficient at infinite dilution requires that activity on the scales of volume concentration (M, N, or c) and on the molal (m) scale shall be related by $\mathbf{a}_M = \mathbf{a}_m \mathrm{d}^0$, where d^0 is the density of water. Thus, for a given solution,

$$(\mathrm{paH})_m - (\mathrm{paH})_M = \log \mathrm{d}^0$$

At temperatures below 25°C., paH values on the two scales differ by 0.001 or less. At 60°C. the difference is 0.007, and at 100°C., 0.019. The value of E^0 likewise reflects a change in standard state and scale of concentration. Hereafter the molal scale will be used. All values of E.M.F. are given in international volts.

tion of the scale will depend upon whether an attempt is made to evaluate the potential difference at the liquid junction and the manner in which the evaluation or correction is made. In the use of cell II to determine differences of $-\log a_H$, as is usually done, the problem is formally simplified but remains unsolved. A consideration of the thermodynamics of the cell reveals why this is so.

The chemical reaction in cell II, apart from ion transfer across the liquid junctions, is

$$\tfrac{1}{2}H_2(g) + \tfrac{1}{2}Hg_2Cl_2(s) = Hg(l) + H^+ \text{ (in solution 1)} + Cl^- \text{(in 0.1 } N \text{ KCl)} \tag{7}$$

The observed E.M.F. of the cell, E, corrected to a partial pressure of 760 mm. of hydrogen, is given by

$$E = E^0 - \frac{2.303RT}{\mathrm{F}} \log a_H a_{Cl} + E_j \tag{8}$$

or

$$\frac{\mathrm{F}(E - E^0 - E_j)}{2.303RT} = \mathrm{paH} - \log a_{Cl} \tag{8a}$$

where E_j is the algebraic sum of the liquid-junction potentials. It should be noted that E^0 now refers to the standard state of unit activity instead of unit concentration. It is the electromotive force of a hypothetical cell of type II, corrected for the liquid-junction potential, in which each of the reactants and products of the cell reaction is present at unit activity.

In equation 8, a_H represents the activity of hydrogen ion in solution 1, and a_{Cl} is the activity of chloride ion in the solution of potassium chloride in contact with the calomel electrode. Hence $a_H a_{Cl}$ is not accessible to direct measurement, and E_j cannot be obtained from equation 8. Furthermore, E_j can never be calculated without an extrathermodynamic assumption to relate the activity coefficients of the ions. Partial corrections, made without consideration of the activity coefficients of ions transferred across the boundary, may in unfavorable instances even be worse than no corrections (43). Accurate determinations of $-\log a_H$ by means of concentration cells with transference are, however, possible under certain conditions with the aid of the Debye–Hückel limiting law in the region of its validity (at ionic strengths of 0.002 or below).[4] In certain special cases, a function of the electromotive force can be extrapolated to a limiting condition that is amenable to thermodynamic treatment (120, 121, 122). The difference of paH between two solutions is, by equation 8a,

$$\frac{\mathrm{F}(E_1 - E_2)}{2.303RT} = (\mathrm{paH})_1 - (\mathrm{paH})_2 + \frac{\mathrm{F}(E_{j_1} - E_{j_2})}{2.303RT} \tag{9}$$

---

[4] Kortüm (93) has discussed this method of calculating the liquid-junction potential and the related experiments of Hermans (71, 72, 73). Unfortunately, only the potential at the interface between simple solutions of the same electrolyte can be obtained, and the ionic strengths must be extremely low. In this connection, the computation of diffusion potentials and ionic activity coefficients described by Szabó (155, 156, 157) is of interest.

If the last term of equation 9 can be reduced to small values, a difference of paH can be obtained. Standardization of the cell with a solution of known or assigned paH then makes it possible to compute the paH of the second or unknown solution.

The activity of chloride ion, a_{Cl}, in equation 8a is unknown. It is constant, however, when the same reference electrode is used. For this reason it will be convenient to define a quantity, $E^{0\prime}$, as follows:

$$E^{0\prime} \equiv E^0 - \frac{2.303RT}{\mathrm{F}} \log a_{Cl} \qquad (10)$$

From equations 8a and 10 we have

$$\mathrm{paH} = -\log f_{\mathrm{H}} m_{\mathrm{H}} = \frac{\mathrm{F}(E - E^{0\prime} - E_j)}{2.303RT} = \frac{E - (E^{0\prime} + E_j)}{k} \qquad (11)$$

and the equivalent expression,

$$E^{0\prime} + E_j = E - k\,(\mathrm{paH}) \qquad (11a)$$

The symbol k will be written for $2.3026RT/\mathrm{F}$. At 25°C., equation 11 becomes[5]

$$\mathrm{paH} = \frac{E - (E^{0\prime} + E_j)}{0.05914} \qquad (12)$$

The form of equation 12 is identical with that of equation 4.

Use of equations 11 and 12 to determine the paH of so-called unknowns entails the use of previously determined values of $E^{0\prime} + E_j$ or a redetermination of $E^{0\prime} + E_j$ at the time of measurement by calibration of the cell with a reference solution of known or assigned paH (equation 9). These two procedures will receive further attention in a later section. The equality of the potential difference across the junctions, reference|KCl and unknown|KCl, is implied in both.

A 3.5 *M* solution of potassium chloride or saturated solution (4.80 *m* or 4.16 *M* at 25°C.) is customarily interposed between the unknown solution and the reference electrode of cell II in an attempt to reduce the magnitude of the junction potentials, and presumably the differences among the potentials, between potassium chloride and the many different solutions that are employed as standards and unknowns. A concentrated solution of ammonium nitrate is not as effective as saturated potassium chloride for this purpose (15), but mixed chlorides and nitrates appear to possess certain advantages (106). The bridge solution of potassium chloride is often regarded as reducing the residual liquid-junction potential to a few tenths of a millivolt, when the pH of each solution forming the boundary is greater than 3 and less than 11 (88, 123).

The inequalities among the mobilities of ions other than hydrogen and hydroxyl are not large. When the buffer solution is neither strongly acid nor strongly alkaline, the concentrations of these excessively mobile ions are negligible. The tendency is toward a small, though constant, diffusion potential rather than complete elimination of it (25).

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[5] Values of k at other temperatures can be found in reference 105.

Inasmuch as the equality of the potentials at the interfaces between a saturated solution of potassium chloride and two different buffer solutions can never be affirmed, a series of buffer standards of known paH (if these values can be assigned) will yield a scale for the most part lacking in thermodynamic rigor. The residual error in paH, equal to $(E_{j_1} - E_{j_2})/0.05914$ at 25°C., cannot readily be avoided. Bjerrum (14, 15) has attempted to eliminate the diffusion potential by using both 1.75 M and 3.5 M potassium chloride as bridge solutions in cell II. The observed difference in electromotive force was employed as an extrapolation term to render the elimination more complete than could be obtained with a saturated solution of potassium chloride alone.

Sørensen and Linderstrøm-Lang (153) found that the Bjerrum extrapolation gave substantially the same result as the interposition of saturated potassium chloride, so long as the solutions studied were neither very acid nor very alkaline. Only when the observed difference of electromotive force is small is there justification for assuming that the liquid-junction potential has been eliminated by the Bjerrum extrapolation (2, 18). A solution formed by saturating the electrode liquid with potassium chloride has sometimes been interposed between the electrode liquid and the bridge of saturated potassium chloride in an attempt to reduce the liquid-junction potential (111, 112). In his monograph, Clark advocated the universal use of the bridge solution of saturated potassium chloride and the abandonment of all attempts to correct the electromotive force for diffusion potentials in the determination of psH (25). Michaelis (110), in recommending the use of saturated potassium chloride, admits the possible advantage of the Bjerrum extrapolation in measurements of solutions in which the concentration of hydrogen ion or hydroxyl ion exceeds 0.001 gram-ion per liter.

III. PH SCALES WITH THERMODYNAMIC SIGNIFICANCE

All thermodynamic methods yield mean activity coefficients, $f_\pm$, and not ionic activities. A scale of paH must therefore embrace a non-thermodynamic formula which permits an ionic activity coefficient to be derived from an experimentally determined combination of activity coefficients of two or more ionic species. A plausible separation for dilute solutions of a uni-univalent electrolyte is

$$f_+ = f_- = f_\pm \tag{13}$$

For some standard buffer solutions, in which the total salt concentration may exceed 0.1 m, such an assumption is certainly not justified.

The definition of a unit of acidity, ptH, with thermodynamic meaning,

$$\text{ptH} \equiv -\log m_{\text{H}} f_\pm \tag{14}$$

avoids a part of this difficulty. Equation 14 is formally less objectionable than equation 5. The ptH value has significance, however, only in those solutions for which the mean activity of acid can be measured or calculated, and this is not always a simple task. In mixtures, the term "mean activity coefficient of acid" is ambiguous, unless the particular anion to be associated with the hydrogen ion is specified. The ptH value is evidently related to paH by

$$\text{ptH} = \text{paH} + \log (f_{\text{H}}/f_\pm) \tag{15}$$

Hitchcock (74) has suggested the use of cells without liquid junction of the type,

$$H_2; \begin{matrix}\text{solution}\\ \text{containing Cl}^-\end{matrix}, AgCl; Ag \qquad \text{Cell III}$$

for the determination of acidity. The unknown solution must contain chloride ion in an amount known within 1 per cent, if an accuracy within a few thousandths of a pH unit is to be attained. It must also be free of substances that disturb the potential of the silver–silver chloride electrode (126) or that are catalytically reduced at the hydrogen electrode (46). The solution should preferably be free of dissolved air (147).

The electromotive force of cell III is given by

$$\frac{\mathbf{F}(E - E^0)}{2.3026RT} + \log m_{\text{Cl}} = -\log (f_{\text{H}} f_{\text{Cl}} m_{\text{H}}) \tag{16}$$

Guggenheim (34) and Hitchcock (74) have pointed out the advantage of a unit of acidity which will be called pwH,

$$\text{pwH} \equiv -\log (f_{\text{H}} f_{\text{Cl}} m_{\text{H}}) \tag{17}$$

and which can be determined exactly from measurements of cell III or a similar cell without liquid junction. This unit retains its significance at high ionic strengths. Inasmuch as pwH is $-\log (m_{\text{H}} f^2_{\text{HCl}})$, where f_{HCl} is the mean activity coefficient of the ions of hydrochloric acid, it differs numerically from paH and ptH in solutions of moderate concentration.

The scale defined by equation 17 in terms of the electromotive force of cell III would appear to solve many of the uncertainties of pH measurement. In a great number of instances, however, this procedure is impractical. The cell with liquid junction, in spite of its theoretical difficulties, remains the most convenient and widely used means for measuring the acidity of aqueous solutions.

The approximate relationships among paH, psH, and pcH are given by

$$\text{paH} = \text{psH} + 0.04 = \text{pcH} + \phi(\mu) \tag{18}$$

where $\phi(\mu)$ represents some function of ionic strength The appearance of this last term in equation 18 emphasizes the fact that there can be no constant difference between a_{H} and c_{H}. The relationships among these three scales and the pwH scale are shown in figure 1, where the pH values of acetic acid–sodium acetate mixtures at 25°C. are plotted as a function of concentration.

Let us examine further the nature of pwH. Combination of equation 17 with the mass-law equation for the dissociation of a weak acid, HA, gives

$$\text{pwH} = \text{p}K - \log (m_{\text{HA}}/m_{\text{A}}) - \log (f_{\text{HA}} f_{\text{Cl}}/f_{\text{A}}) \tag{19}$$

where pK is the common logarithm of the reciprocal of K, the dissociation constant. When HA is a monobasic acid, the last term of equation 19 is small. If, further, the buffer ratio is unity, pwH is approximately equal to pK at all concentrations. The upper curve of figure 1, calculated from the author's measurements of cells of type III, illustrates the approximate constancy of pwH for mixtures of acetic acid and sodium acetate. The pwH values are, however, about 4.76, or slightly greater than pK, which is 4.756 at this temperature (56). Obviously this constancy detracts from the usefulness of pwH as a practical unit of acidity. As shown in figure 1, a change of 30 per cent in the hydrogen-ion concentration (0.16 in pcH) has no perceptible effect upon pwH. When HA is the primary or secondary anion of a dibasic or tribasic acid, pwH changes with ionic strength, but less sharply than do pcH, paH, and psH.

The paH and psH numbers were computed from E.M.F. measurements of hydrogen–calomel cells with liquid junction (36, 76, 102) by equations 4 and 12 with the aid of published values of $E^{0\prime} + E_j$ (76, 102). In the evaluation of pcH from paH, it was assumed that f_H at a particular ionic strength, μ, could be computed from the Debye–Hückel equation (29), written as follows:

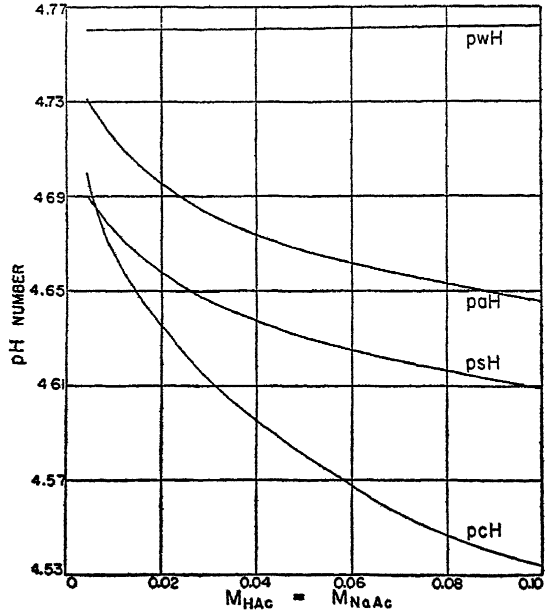

FIG. 1. pH values for acetate buffers on four different scales as a function of concentration at 25°C.

$$-\log f_H = 0.509\sqrt{\mu}/(1 + 1.3\sqrt{\mu}) \tag{20}$$

At infinite dilution, pcH and paH are, of course, identical. Before that limit is reached, however, the solute is so attenuated that the acid is highly dissociated and the buffering action largely disappears. The pH of the solution then approaches that of the solvent alone.

The simple expressions for computing psH and paH (equations 4 and 12) are of the same form. It is evident that a change in $E^{0\prime} + E_j$ (equations 11 and 12) results in a shift of the pH scale. By choice of a suitable value for this potential, the pH number computed from the same electromotive force can be made to conform to the scale of either psH or paH. Table 1 lists these values of $E^{0\prime} + E_j$ for cell II and for the corresponding cell with a saturated calomel electrode:

H_2; solution 1 | KCl (satd.), Hg_2Cl_2; Hg Cell IV

IV. CHOICE OF A STANDARD pH SCALE

The pH measurement of unknown solutions by means of cells with liquid junction always involves an uncertainty of 0.02 unit or more, as a consequence of the unknown residual liquid-junction potential. The consistent use of a single standard scale by all investigators will result, however, in elimination of the differences among scales. Figure 1 shows that these differences may amount to 0.04 to 0.1, or even more at high ionic strengths. Only when pH is referred, by general agreement, to a single value of $E^{0\prime} + E_j$ at a particular temperature, or to a single series of standards, will the present confusion be lessened (51).

TABLE 1

Values of $E^{0\prime} + E_j$ for different pH scales at 25°C.

SCALE UNIT	$E^{0\prime} + E_j$	
	Cell II	Cell IV
	volts	*volts*
pcH	About 0.3400*	About 0.2488*
psH	0.3376	0.2464
paH, ptH	0.3353 to 0.3358†	0.2441 to 0.2446†

* Computed from the data of Hitchcock and Taylor (76) for 0.1 *M* hydrochloric acid and a mixture of 0.01 *M* hydrochloric acid with 0.09 *M* potassium chloride. $E^{0\prime} + E_j$ can have no constant value for the pcH scale.

† References 76 and 102.

The Sørensen scale and other "conventional" scales that are based upon neither c_H nor a_H serve satisfactorily for reproducible comparisons of the results of different workers. Yet pH is used extensively in rough quantitative calculations involving chemical equilibrium. The engineer and chemist need to know insofar as possible the character of the quantity being measured. Scales of pcH, paH, and ptH answer these requirements in greater or less degree.

The lack of agreement on the most suitable scale of acidity stems from the far-reaching influence of hydrogen ion upon diverse chemical phenomena. It would not be surprising to learn, for example, that investigators of catalysis and of the kinetics of reactions preferred to know the hydrogen-ion concentration of of the solutions with which they work. Likewise, the activity of hydrogen ion would prove of considerable usefulness in studies of chemical equilibrium and electrodeposition. In many instances, $m_H f_{\pm}^2$ is of importance (34). The negative logarithm of this quantity has the same dimensions as pwH. Although pwH retains its significance at high ionic strengths, there are objections to its general use as a unit of acidity, as we have indicated.

Insofar as they are based upon values of $E^{0\prime} + E_j$ (equation 11) found by extrapolation to zero ionic strength where equation 13 obtains, paH and ptH are numerically equal. Guggenheim has pointed out (34) that cells of types II and IV, and thus the pH meter, measure a quantity which might be designated $c_H f_?$, where $f_?$ is much more complicated than $f_\pm$, inasmuch as it depends upon transport numbers of the ions in the cell. Neither f_H nor $f_\pm$ can be derived from $f_?$, and any practical standardization of paH or ptH will be theoretically unsatisfactory.

There remains the possibility of computing the hydrogen-ion concentration (c_H or m_H) of a buffer solution accurately (54, 75, 82). In this matter the optical method can offer considerable help (40, 41, 81, 83). The determination of m_H could not, however, be applied conveniently to unknown mixtures.[6]

A change of $E^{0\prime} + E_j$ in equation 12 effects the upward or downward displacement of curves such as those of paH and psH (figure 1). Evidently it would be impossible to calculate pcH from a simple equation of the form of equation 11. To do this a knowledge of f_H is required, and the ionic strength must be known before f_H can even be estimated.

Although the importance of the hydrogen-ion activity in chemical equilibria has been widely recognized, there has been some reluctance to abandon the conventional psH scale. Thus Sørensen and Linderstrøm-Lang (153) in first defining the activity scale felt it premature to introduce the activity principle in place of the concentration principle generally. However, the psH scale, to which the great mass of published data refers, is unfortunately not a scale of concentration at all. Kolthoff, one of the early advocates of paH (87, 88, 90), recommends the adoption of an activity scale only when standard values shall be recognized internationally (86).

In the past twenty years, however, the situation has become still more confused. It has been urged that attention be directed in published work to the meaning of the pH values and to the details of their determination (25, 114, 115, 143), but this advice appears often to have gone unheeded. The activity scales defined by Hitchcock and Taylor (76, 77) and MacInnes, Belcher, and Shedlovsky (102) have found more and more use, and standards whose paH values are based upon measurements of cells without liquid junctions have been issued by the National Bureau of Standards. Furthermore, the initial step toward international endorsement of the activity scale has been taken (148). Nevertheless, many pH measurements are still based on the conventional scale defined by Sørensen.

Some eight years after the appearance of the third edition of his widely used monograph, Clark, in a discussion of the nature of the pH scale, wrote (26), "... we can remove some confusion by doing away with its form and preserving its substance." The possibility of employing an electromotive force, as in oxidation–reduction systems, or the Gibbs chemical potential in place of pH numbers was considered. Clark suggests that the latter quantity, closely allied to paH, might be derived from the electromotive force of cells without liquid junction. The fundamental difficulty of determining the activity coefficient of a single species will, in his view, "be met by sensible adjustments to approximation theory."

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[6] Kilpatrick and coworkers (81, 82, 83) have compared the colorimetric, electrometric, and catalytic methods for determining m_H in benzoate and acetate buffer solutions with added potassium chloride and have obtained concordant results up to an ionic strength of 2 for the benzoate system and 3 for the acetate system.

The shift from psH to paH involves merely a shift of $E^{0\prime} + E_j$ by an amount which corresponds approximately to an increase of 0.04 in pH (compare equation 12 and figure 1). The psH has virtually no meaning. The paH value has in itself no significance in terms of physical reality, yet its rôle in chemical equilibria is simply and unequivocally defined. For these reasons, the general adoption of the activity scale seems warranted.

V. PRIMARY AND SECONDARY STANDARDS

Examination of the problem of calculating paH from the electromotive force of cells with liquid junction reveals that the precision of a series of measurements, which are essentially comparisons with a standard of assigned paH value, can be enhanced by use of several standards of different paH. For the control laboratory, this procedure is of advantage in reducing errors imparted by differences in temperature and by the wrong adjustment of a pH meter to the theoretical slope of pH with respect to electromotive force (10). Calibration with two buffer solutions of different pH is also of value in demonstrating the proper functioning of the electrodes. The accurate examination of strongly alkaline solutions, where the glass-electrode error is a factor, requires especial care in the selection of buffers (30). It is obviously important that these standards be consistent with each other and define a paH scale that is uniform over its whole range.

The commonly used pH standards are solutions that can be easily prepared from pure, stable, crystalline buffer salts. These buffer solutions are of varying types and compositions. The definition of a uniform paH scale in terms of all of these standards is difficult, inasmuch as the specific behaviors and individual characteristics of ions disappear only at dilutions so great as to be generally inaccessible to experiment. The usefulness of two series of standards is thus apparent. The first group would be composed of primary standards of similar composition and low concentration, whose paH values could be closely fixed. Other convenient secondary, or practical, standards, composed of stable buffer salts of different types and concentrations, would make up the second group. The primary standards would serve for a determination of $E^{0\prime} + E_j$. The paH of the secondary standards would be determined by careful comparison with the primary group.

Specifications for standardizing practical pH measurements have been set forth by Clark in his monograph (25). These directions would be modified only by the substitution of a new set of values of $E^{0\prime} + E_j$, consistent with the primary paH standards. No correction for the liquid-junction potential is necessary. As yet no standard potentials applicable to all strong acid–salt mixtures or to strong bases can be recommended. If there is any departure from standard procedure in the determination of the pH values included in published material, a statement of the essential modifications should be made.

In the sections to follow, some possible methods of establishing a uniform series of primary standards and assigning to them acidity values that closely approximate $-\log a_H$ will be compared. The calculation of paH from E.M.F. measurements of hydrogen–calomel cells with transference will be considered first.

VI. THE HYDROGEN–CALOMEL CELL WITH LIQUID JUNCTION

It has been seen that the activity scale appears to be the most generally useful one for measuring the acidity of aqueous solutions. We shall now consider means of standardizing electrometric pH instruments to yield values that correspond as closely as possible to this scale. As pointed out in an earlier section, there are two methods of approach: choice of $E^{0\prime} + E_j$, or evaluation of the paH values of one or more standard reference solutions.

A. The liquid-junction potential

The paH value is usually derived from the electromotive force of cells of types II or IV. The cell with saturated calomel electrode is generally used in the pH meter, and the hydrogen electrode is replaced by the versatile glass electrode. The electromotive force of the cell with liquid junction is a complicated function of the concentrations and transference numbers of each ionic species present in the electrode solutions and in the transition layers which form the boundary (85). The potential, E_j, at the liquid junction between two solutions I and II is given by

$$E_j = -k \int_{\mathrm{I}}^{\mathrm{II}} \sum (T_i/z_i)\, \mathrm{d} \log f_i m_i \tag{21}$$

where T_i is the transference number of the ion whose valence is z_i and the summation is made for all ions in the boundary.

As has often been pointed out (36, 52, 100, 139, 159), the evaluation of individual ionic activity coefficients requires an exact knowledge of E_j, and the value of E_j, in turn, rests upon a knowledge of the ionic activity coefficients. The electric potential difference between two points in different media has not yet been defined in terms of physical realities (32, 33), and the activity coefficient of an ion is not an experimental quantity but a mathematical device (159). MacInnes regards as extreme the view that single ion activities have no physical meaning (101) and points to their usefulness as mathematical concepts in visualizing cell mechanisms. The problem of computing E_j is, however, incapable of solution unless an assumption from outside the realm of thermodynamics is introduced.

One of the common assumptions, that suggested by MacInnes (99), asserts the equality of the activity coefficients of the ions of potassium chloride in a pure solution of the salt of any concentration. The ionic activity coefficient is assumed not to be influenced by the presence of other ions with which the ion in question may be associated in other mixtures where the same concentration of the ion is maintained. Thus the chloride-ion activity is considered to be the same in a solution of any chloride as in a solution of potassium chloride of the same chloride concentration. The activity coefficients of the ions of uni-univalent electrolytes have often been set equal to the mean activity coefficients. In other words, the validity of equation 13 at all ionic strengths is assumed. Although used earlier by others, this second assumption was generalized by Guggenheim and is now usually associated with his name.

Either of these postulates makes possible a calculation of the potential difference across junctions the structure of which corresponds to certain models, provided that the mean activity coefficients of the electrolytes and the transference numbers of the ions in the mixtures composing the transition layers are known. Nevertheless, the calculation is awkward at best, and the necessary information is not usually available. In spite of these limitations, the liquid-junction potentials that can be computed for certain simple cases from available experimental data and non-thermodynamic assumptions are not at all unreasonable. For this reason, the calculation deserves further consideration here.

The liquid-junction potential given by equation 21 can be separated into an ideal part, E_m, and a non-ideal part, E_f:

$$E_j = E_m + E_f \tag{22}$$

The equations of Henderson (69, 70) and Planck (124) yield only the ideal term, E_m. No activity coefficients are used in calculating E_m, and consequently no assumption, apart from the character of the distribution of the ions in the boundary, is involved. When strong acids are present at concentrations up to 0.1 M, E_f may amount to a third of E_j, or more. Hamer's calculation (42) by the graphical method of Harned (52) suggests that E_f may be only 0.1 to 0.2 mv., or about 5 per cent of E_j, when the junction is formed between saturated potassium chloride and acetate buffers. Unfortunately, the computation of E_j is markedly affected by errors in the transference numbers (18, 36), and too few data are available to demonstrate whether E_f is likewise small when other weak acid systems are involved.

MacInnes and Longsworth (101, 103) found essentially the same values for the potentials at the junctions between different concentrations of the same electrolyte—sodium chloride, potassium chloride, or hydrochloric acid—regardless of whether the computations of ionic activity coefficients were based upon the MacInnes or the Guggenheim assumptions. In this connection, it should be remembered that the manner in which the junction is formed has little effect upon E_j when the boundary is formed between different solutions of the same electrolyte. It has been shown (42, 103) that the calculated E_j for the junction: HCl (0.1 M) | KCl (satd.) is 2.0 mv. when the computation is based on the Guggenheim assumption, and 2.8–2.9 mv. on the MacInnes assumption. It makes a decided difference which convention is adopted. The assumed structure of the boundary has little influence, however, on the calculated potential of the cell. Junctions formed from potassium chloride and a buffer solution are still more complex, and the computation of E_m requires information or assumptions regarding the distribution of the electrolytes in the transition layers. The equations are therefore of little practical value in the determination of the pH of a reference buffer for pH standardization. As we shall see, practical standardizations of the hydrogen–calomel cell need not involve a calculation of the liquid-junction potential.

B. Previous standardizations of the paH scale

It is evident that E^0 in equations 8a and 10 is the negative of the standard potential of the mercury–mercurous chloride electrode. The value of E^0 is found to be 0.2679 v. at 25°C. by adding 0.0455 v., the electromotive force of the silver chloride–calomel cell without liquid junction (31, 128), to 0.2224 v., the standard potential of the hydrogen–silver chloride cell (58). Both the MacInnes assumption and the Guggenheim assumption justify the substitution of a_{KCl}, the product of the molality of potassium chloride at the calomel electrode and its stoichiometrical activity coefficient, for a_{Cl} in equation 10. The molalities of potassium chloride in the 0.1 N and saturated solutions are, respectively, 0.1005 and 4.804 (140). If we accept the values 0.769 and 0.588 for the activity coefficient of potassium chloride in these solutions (55, 140, 146), we find by equation 10 that $E^{0\prime}$ is 0.3337 v. for the 0.1 N calomel electrode and 0.2412 v. for the saturated calomel electrode. This same value of $E^{0\prime}$ for the cell with hydrogen electrode and the 0.1 N calomel electrode was chosen by Guggenheim and Schindler (36) and by Hamer (42). The former based their choice wholly, and the latter in part, upon the explicit assumption of a relationship between a_{Cl} and a_{KCl} such as we have used here.

Equation 11 may be regarded as a conventional definition of f_H and of $E^{0\prime} + E_j$. The value of one depends on the value assigned to the other. It is evidently possible to measure the electromotive force of cell II or IV when solution 1 contains only strong acids (so that m_H is known), to evaluate f_H from the known mean activity coefficients and an assumption such as those of MacInnes and Guggenheim, and thus to calculate $E^{0\prime} + E_j$. Each different value of $E^{0\prime} + E_j$ constitutes a different basis for a scale of paH.

Guggenheim and Schindler (36) chose $E^{0\prime} = 0.3337$ v. as the basis of their paH scale, because this potential was found to yield values for f_H (equation 11) in 0.1 M hydrochloric acid and in mixtures of 0.01 M hydrochloric acid with 0.09 M sodium and potassium chlorides that were nearly the same as those calculated with the aid of the MacInnes convention. The Henderson equation was used to compute E_j. It is readily shown that the Guggenheim convention would have led to a value of 0.3329 v. From the paH values given by Guggenheim and Schindler for three acetate buffers and three phosphate buffers, we find by equation 11a an average $E^{0\prime} + E_j$ of 0.3345 ± 0.0005 v.

Electromotive-force measurements of hydrochloric acid and buffer solutions of acetates were shown by Hamer (42) to lead to approximately the same value of $E^{0\prime}$ (0.3337 v.) as that given above for cell II. For the cell with a saturated calomel electrode (type IV), the strong acids yield 0.2407 v., whereas buffered solutions give 0.2414 v. Two values of $E^{0\prime} + E_j$ were chosen for each of the two types of cell. The contributions of both E_m and E_f to the liquid-junction potential (compare equation 22) were considered. The computation of E_j was based on the MacInnes assumption. Of the two values for cell II, 0.3369 v. was intended to apply to measurements of solutions that contained strong acids, and 0.3346 v. was recommended for measurements with buffered solutions that contain weak acids.[7] Experimental evidence furnishes ample support for such a dual set of values. Actually, $E^{0'} + E_j$ for various mixtures containing strong acids appears to vary too widely to permit the paH of all mixtures of that class to be calculated with the use of any single value of the standard potential.

Sørensen and Linderstrøm-Lang (153), in defining the first scale of paH, based their choice of the standard potential of cell II upon an extensive series of electromotive-force measurements of cells that contained mixtures of hydrochloric acid and sodium or potassium chloride. Each measured E.M.F. value was corrected for the liquid-junction potential by means of the Bjerrum extrapolation. The activity coefficient of the hydrogen ion was computed by Brønsted's equation (22) and the earlier cube-root formula of Bjerrum (16). A value of 0.3357 was selected for $E^{0'}$ at 18°C. At 25°C., $E^{0'}$ becomes 0.3353 v. It was suggested that the Bjerrum extrapolation be employed in measurements of paH. In later work (154) these authors themselves used a bridge of saturated potassium chloride between buffered solutions and the reference electrode and made no correction of the measured electromotive force. It is possible, however, that Sørensen and Linderstrøm-Lang would retain the extrapolation procedure in measurements with mixtures containing strong acids. If we are to assume that they intended the same standard potentials as were recommended in their earlier paper (153) to apply to measurements of buffered solutions by their later procedure, $E^{0'} + E_j$ is 0.3353 v.

Substitution of a solution of potassium chloride saturated at 25°C. for the 3.5 *M* bridge solution appears to alter the electromotive force of cell II by only 0.1 mv. (42). For this reason, the concentration of the bridge solution will not usually be specified, so long as it is 3.5 *M* or greater.

Scatchard (136) assumed an unchanging potential across a flowing junction between a saturated solution of potassium chloride and solutions of hydrochloric acid as the concentration of the latter was reduced from 0.1 *M* to zero, in which limit f_H is unity by definition. Electromotive-force measurements of cells of the type,

$$\text{Ag; AgCl, HCl } (m) \mid \text{KCl (satd.), Hg}_2\text{Cl}_2\text{; Hg} \qquad \text{Cell V}$$

were made, and E', that is, $E + k \log m$, was plotted as a function of the square root of the molality and the limiting value at zero concentration obtained. Addition of 0.2226 v., the standard potential of the hydrogen–silver chloride cell (135), gave 0.2454 v. for $E^{0'} + E_j$ (cell IV) at 25°C. Inasmuch as this treatment of the cell with liquid junction requires no *a priori* statement relating the ionic activity coefficients, Scatchard was able to compute f_H and f_{Cl} in the solutions of hydrochloric acid used in the cells. These experimental activity coefficients were in excellent accord with those based upon the MacInnes assumption at concentrations of acid not exceeding 0.2 molal.

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[7] The potentials recorded in the last column of table VI of Hamer's paper refer to the cell in which the junction is made directly between 0.1 *N* potassium chloride and solution 1 without interposition of saturated potassium chloride. The values of $E^{0'} + E_j$ given here for cell II were therefore computed from the corresponding potentials of cell IV, given in column 2 of the same table, by addition of 0.0912 v. (102).

The assumption of an unchanging liquid-junction potential and the validity of Scatchard's extrapolation are open to question (30). It is of interest, however, that a later determination of $E^{0'} + E_j$ from similar measurements (76), with the employment of the Debye–Hückel equation in the extrapolation, led to a value, 0.2450 v., in reasonably good agreement with that found by Scatchard. If the most recent value of E^0 for the hydrogen–silver chloride cell (58) is combined with Scatchard's extrapolated value for cell V, $E^{0'} + E_j$ becomes 0.2452 v., and the agreement of the two investigations is quite satisfactory. Inasmuch as the electromotive force of the cell,

$$\text{Hg; Hg}_2\text{Cl}_2\text{, KCl (satd.)} \mid \text{KCl (0.1 } N\text{), Hg}_2\text{Cl}_2\text{; Hg} \qquad \text{Cell VI}$$

has been found to be 0.0912 v. at 25°C. (18, 102, 130), we are able to compute $E^{0'} + E_j$ for cell II from the corresponding quantity for cell IV. Addition gives 0.3364 v. for this potential.

By measurement of the electromotive force of a concentration cell with transference, Kolthoff and Bosch (90) concluded that a paH value of 2.075 should be assigned to the standard reference mixture, 0.01 *M* hydrochloric acid and 0.09 *M* potassium chloride. This reference solution was compared experimentally with a solution of hydrochloric acid so dilute (0.001 *M*) that f_H would be practically identical with the known mean activity coefficient of the acid. A correction was made for E_m, the ideal part of the diffusion potential. The E.M.F. of cell II with 0.01 *M* hydrochloric acid and 0.09 *M* potassium chloride as solution 1 is 0.4583 v. at 25°C. This is the mean of three closely agreeing measurements, 0.45830 found by Guggenheim and Schindler (36), 0.4584 by Bjerrum and Unmack (18), and 0.4582 computed from the E.M.F. of cell IV given by Hitchcock and Taylor (76). From equation 11a, therefore, $E^{0'} + E_j$, the basis of Kolthoff's paH scale (90, 91), is found to be 0.3356 v.

Bjerrum and Unmack (18) based their computation of paH on an extensive series of electromotive-force measurements for which solutions of hydrochloric acid and mixtures of hydrochloric acid with sodium and potassium chlorides were used in cells of type II. Similar data of other investigators were critically examined. Each electromotive-force value was corrected by means of the Henderson equation for E_m, the ideal part of the liquid-junction potential. The determination of $E^{0'}$ was made by a double extrapolation, as follows: The limiting value of $E + k \log c_H$ at zero acid concentration was first determined for each of several series of acid–salt mixtures of constant total concentration, c. These quantities were then plotted as a function of c, and $E^{0'}$, the limit at $c = 0$, was obtained by extrapolation with the aid of the Debye–Hückel equation. An examination of the data of Bjerrum and Unmack confirms the observation of Hitchcock and Taylor (76) that these three types of solutions yield somewhat divergent results for $E^{0'} + E_j$ and that the difficulty is not remedied by a correction for E_j, or at least for the ideal term, E_m. Nevertheless, Bjerrum and Unmack chose $E^{0'} = 0.3360$ v. at 25°C. as most generally applicable to measurements of all types of solutions. From their paH values for several phosphate and citrate buffer solutions, $E^{0'} + E_j$ is found by equation 11a to be approximately 0.3364 v.

Two solutions that contained hydrochloric acid, four buffer solutions, and a solution of calcium hydroxide were studied by Manov, DeLollis, and Acree (108) by measurements of cells of types III and IV. A silver–silver chloride electrode immersed in an air-free saturated solution of potassium chloride was substituted for the saturated calomel electrode of the latter cell. The paH values of the seven solutions were computed from the electromotive force of the cell without liquid junction with the aid of earlier data for the phthalate, phosphate, phenolsulfonate, and borate systems (6, 12, 47, 107). The values of $E^{0'} + E_j$ for cell II can be obtained by adding 0.0455, the difference between the standard potentials of the calomel and silver–silver chloride electrodes (31), and 0.0912, the E.M.F. of cell VI, to $E^{0'} + E_j$ computed by these investigators. In this way, $E^{0'} + E_j$ for cell II is found to be 0.3358 v. for the solutions of strong acid, 0.3346 ± 0.0004 for the buffer mixtures, and 0.3336 for the solution of calcium hydroxide, a strong base. The fact that moderate concentrations of hydrogen ion effect an elevation of $E^{0'} + E_j$ above the value found with solutions whose pH is between 3 and 11 is well recognized. It is, therefore, not at all surprising to find that the excessively mobile negative ion, hydroxyl, lowers the value of $E^{0'} + E_j$.

Cohn, Heyroth, and Menkin (28), in an analysis of E.M.F. data for mixtures of acetic acid and sodium acetate, demonstrated the influence of a change in $E^{0'} + E_j$ on the determination of pK for acetic acid. "Apparent" pK values at finite concentrations were computed from the measured paH by the mass-law equation. The true pK was obtained by extrapolation to infinite dilution, with the aid of the Debye–Hückel equation. When 0.3380 v. was used for $E^{0'} + E_j$ at 18°C., pK was found to be 4.730, and when 0.3360 v. was used a value of 4.765 resulted. In order to obtain the true pK, 4.757 at 18°C. (56, 57), it would therefore be necessary to use $E^{0'} + E_j = 0.3365$ v. At 25°C., this potential becomes 0.3361 v. (25).

By a similar procedure, Kauko and coworkers (79, 80) assigned different paH values to the reference solution, 0.01 M hydrochloric acid, 0.09 M potassium chloride, and determined the resultant effect upon pK for the first dissociation step of carbonic acid. In this way they chose 2.087 as the correct paH of the reference solution. If E for cell II is again taken as 0.4583 v. at 25°C., $E^{0'} + E_j$ is found by equation 11a to be 0.3350 v.

Two other scales based upon thermodynamic dissociation constants deserve consideration in some detail. The first of these is based upon the work of Hitchcock and Taylor (76, 77), who measured the E.M.F. at 25°C. of cells of type IV containing acetate, phosphate, borax, and glycolate buffer solutions at each of several dilutions. Cells of the type,

$$H_2;\ \text{buffer solution}\ |\ KCl\ (\text{satd.})\ |\ HCl\ (0.1\ M);\ H_2 \qquad \text{Cell VII}$$

were also measured at 38°C. Several concentrations of acetates, phosphates, and borax comprised the buffer solutions used in the half-cell on the left. Measurements of cell VII, for which the buffer solution was replaced by (*a*) 0.1 *M* hydrochloric acid, (*b*) 0.01 *M* hydrochloric acid and 0.09 *M* sodium chloride, and (*c*) 0.01 *M* hydrochloric acid and 0.09 *M* potassium chloride were made at 25° and 38°C. Additional solutions, formed by diluting these three with water, were also studied.

The second scale is that of MacInnes, Belcher, and Shedlovsky (102), who studied acetate buffer solutions by means of E.M.F. measurements of cell II at 12°, 25°, and 38°C. These data were supplemented by a series of measurements made with chloroacetate buffer solutions at 25°C.

Hitchcock and Taylor used paH, and MacInnes, Belcher, and Shedlovsky ptH, in the formal equations for determining $E^{0\prime} + E_j$. If the buffer solution is composed of a weak monobasic acid, HA, together with its salt, the dissociation constant, K, and the "incomplete" dissociation constant ("unvollständige Dissoziationskonstante" of Bjerrum and Unmack (18)), K', are given by

$$\mathrm{p}K' = \mathrm{p}K + \log \frac{f_{\mathrm{A}}}{f_{\mathrm{HA}}} = \mathrm{paH} - \log \frac{c_{\mathrm{A}}}{c_{\mathrm{HA}}} \tag{23}$$

and

$$\mathrm{p}K' = \mathrm{p}K + \log \frac{f_{\pm}}{f_{\mathrm{HA}}} = \mathrm{ptH} - \log \frac{c_{\mathrm{A}}}{c_{\mathrm{HA}}} \tag{24}$$

where pK and pK' are as usual the common logarithms of $1/K$ and $1/K'$. The two different definitions of the unit of acidity lead to equations of identical form. In either case, pK' is a linear function of the square root of the ionic strength in dilute solutions, and its value at zero ionic strength is pK. As equation 23 shows, the difference between pK' and pK affords a measure of the ratio of the activity coefficients of the buffer components (27, 68).

Hitchcock and Taylor expressed $E^{0\prime} + E_j$ in terms of pK by combining equations 11 and 23. The effect of activity coefficients was removed by extrapolation to zero ionic strength with the use of the Debye–Hückel equation. MacInnes, Belcher, and Shedlovsky employed assumed values of $E^{0\prime} + E_j$ to compute ptH by the right-hand side of equation 11. The corresponding values of pK' obtained from equation 24 yielded a provisional pK by suitable extrapolation. As Cohn, Heyroth, and Menkin (28) have shown, the proper $E^{0\prime} + E_j$ will be that which, by trial, furnishes the known pK.

As a basis for a scale of pH, MacInnes, Belcher, and Shedlovsky found $E^{0\prime} + E_j$ for cell II to be 0.3358 v. at 25°C., 0.3352 v. at 38°C., and 0.3364 v. at 12°C. For the corresponding cell with a saturated calomel electrode (cell IV), $E^{0\prime} + E_j$ is found to be 0.2446 v. at 25°C. by subtraction of 0.0912 v., the E.M.F. of cell VI. In the computation of paH, Hitchcock and Taylor use 0.2441 v. for $E^{0\prime} + E_j$ of the cell with the saturated calomel electrode (type IV). The corresponding value for cell II is 0.3353 v. The two pH scales differ, therefore, by 0.008 unit. These potentials are in acceptable agreement with 0.3353 v., suggested by Sørensen and Linderstrøm-Lang (153, 154) as the basis for a paH scale at 25°C.

These scales achieve some measure of thermodynamic significance without sacrifice of utility. No estimate of diffusion potentials is required. The paH cannot be proved to be consistent with pK, however, at any concentration accessible to direct measurement. The observed change of pK' with ionic strength is, nevertheless, approximately that expected from theory, except for the most dilute buffer solutions. This treatment should yield identical paH and ptH values, and the difference found is probably to be ascribed chiefly to the extrapolation, as we shall see presently. All buffer solutions are not found to yield the same $E^{0'}$, presumably because of marked differences in the mobilities of the ions and, hence, in the liquid-junction potential.

TABLE 2

Standard potentials of cell II at 25°C.

REFERENCE	YEAR	$E^{0'}$	$E^{0'} + E_j$	REMARKS
		volts	*volts*	
Sørensen and Linderstrøm-Lang (153)	1924	0.3353		
Scatchard (136)	1925		0.3364	
Sørensen, Linderstrøm-Lang, and Lund (154)	1927		0.3353	
Cohn, Heyroth, and Menkin (28)	1928		0.3361	
Bjerrum and Unmack (18)	1929	0.3360	0.3364	
Guggenheim and Schindler (36)	1934	0.3337	0.3345	
Hamer (42)	1937	0.3337	0.3346	Buffered solutions
			0.3369	Strong acids
Kauko and Airola (79)	1937		0.3350	
Hitchcock and Taylor (76)	1937		0.3353	Buffered solutions
			0.3362	Hydrochloric acid
MacInnes, Belcher, and Shedlovsky (102)	1938		0.3358	
Manov, DeLollis, and Acree (106)	1945		0.3358	Strong acids
			0.3346	Buffered solutions
			0.3336	Calcium hydroxide

A summary of $E^{0'} + E_j$ is given in table 2. All of the values recorded in the table refer to the cell with the 0.1 N calomel electrode and bridge solution of 3.5 M or saturated potassium chloride (type II) at 25°C. The potentials of the corresponding cell with saturated calomel electrode (type IV) are obtained by subtracting 0.0912 v. from the values listed.

C. Evaluation of $E^{0'} + E_j$ for buffer solutions at 25°C.

It is clearly unfortunate that so much of the E.M.F. work with hydrogen–calomel cells has been confined to solutions of strong acids. Although the hydrogen-ion concentration in such solutions is known, the activity of this ion is as undefined as it is in a buffer solution. A single value of $E^{0'} + E_j$ appears to serve satisfactorily for the pH range 3 to 11 (88, 123). Solutions that contain appreciable amounts of strong acids, however, usually require a somewhat higher value, and scales based exclusively upon strongly acid standards are not accurate over the entire pH range. For this reason, Clark (25) has considered the eventual adoption of a sliding scale of potentials. When the majority of paH determinations involve solutions of weak acids or bases and their salts, it is of unquestioned advantage to utilize a value of $E^{0'} + E_j$ that is based upon measurements of systems of this type (28, 112, 113, 153).

A further analysis of the available electromotive-force data for buffer solutions therefore seems appropriate. For this purpose, the cell measurements of Hitchcock and Taylor (76) were converted, by the addition of 0.0912, to the corresponding data for cell II. Larsson and Adell (95, 96) have studied the effect of neutral salts upon the paH of a large number of monobasic acid buffers at 18°C. by means of electromotive-force measurements of quinhydrone–calomel cells. When their data are corrected for the difference between the potentials of the quinhydrone and hydrogen electrodes it becomes apparent that their calomel electrode was neither the standard 0.1 *N* electrode nor the saturated type. We are able, fortunately, to compute the corresponding electromotive forces for cell II at 18°C. by addition of 0.7870 v., the difference between their measurement for the mixture of 0.01 *M* hydrochloric acid and 0.09 *M* potassium chloride, −0.3312 v., and 0.4558 v. found by Bjerrum and Unmack (18) for the same solution, also at 18°C. The measurements of Guggenheim and Schindler (36) and of MacInnes, Belcher, and Shedlovsky (102) will also be considered.

The paH numbers computed from electromotive-force measurements of cells without liquid junction, or from thermodynamic dissociation constants, become increasingly accurate as the ionic strength decreases. There seems good reason to suppose that the paH so derived is, in most instances, accurate within 0.005 unit at ionic strengths of 0.01 or below. If the Debye–Hückel equation, with ion-size parameter, a_i, arbitrarily chosen as 4 Å. (equation 20), is substituted for $\log f_{A^-}$, the mass law yields the following expression for the paH of a mixture of monobasic acid, HA, and its salt,

$$\text{paH} = \text{p}K + \log \frac{m_A}{m_{HA}} - \frac{A\sqrt{\mu}}{1 + 4B\sqrt{\mu}} \qquad (25)$$

in which the activity of the uncharged acid molecules has been set equal to their molality. The constants A and B vary with temperature (105, 138). In dilute solutions the error in the paH that results from such a choice of a reasonable, though probably incorrect, value for the coefficient of the $B\sqrt{\mu}$ term in the denominator of the last term of equation 25 is unimportant. At intermediate ionic strengths it becomes appreciable.

Guggenheim's equation (35) for the mean activity coefficients of strong uni-univalent electrolytes is

$$-\log f_{\pm} = \frac{A\sqrt{\mu}}{1 + \sqrt{\mu}} + \lambda\mu \qquad (26)$$

This relation represents observed activity coefficients at 0°C. successfully at concentrations up to 0.1 M. At a given ionic strength all specific differences among electrolytes are evidently embodied in the coefficients, λ, of the linear term. If, like $f_{\pm}$, the true activity coefficient of the anion A, f_A, and the approximate value, f'_A, computed from the Debye–Hückel equation with a value of 4 for a_i, can likewise be expressed by Guggenheim's equation, the error, Δ(paH), will be

$$\Delta(\text{paH}) = \log f_A - \log f'_A = (\lambda' - \lambda)\mu \tag{27}$$

The error in paH will therefore be a linear function of ionic strength when the ionic strength does not exceed 0.1.

The results of computations of $E^{0\prime} + E_j$ for cell II by equation 11a are given in table 3. The paH values for phosphate and borax buffers were taken from previous publications (8, 109). In all other cases, paH was computed by equation 25. Standard potentials computed at 18°C. were corrected to 25°C. by subtraction of 0.0004 v. (25).

Some of the data of table 3 are plotted as a function of ionic strength in figure 2. The dotted lines are drawn through the points for acetate solutions (upper line), glycolate solutions (middle line), and chloroacetate solutions (lower line). Some of the results plotted in figure 2 are of doubtful accuracy, and great significance cannot be attached to the relations shown there. The prediction that the error of paH varies linearly with ionic strength seems, however, to be confirmed. At ionic strengths above 0.01, the liquid-junction potential appears to be constant, or also varying in linear fashion. When the ionic strength of the buffer solution is less than 0.01, the situation is somewhat altered and the slopes of the lines change sharply. This discontinuity cannot be ascribed to errors in the calculated paH. It is possible that the liquid-junction potential changes rapidly with concentration when the buffer is very dilute.

It must be remembered that, apart from their aid in the establishment of a linear plot, the calculated values of paH, and hence of $E^{0\prime} + E_j$, have little meaning above an ionic strength of 0.01. With the exception of the data for phosphates, which appear to be higher than those of the other buffer systems, the curves of $E^{0\prime} + E_j$ as a function of ionic strength converge well at 0.01 μ, where the calculation of paH is fairly reliable. In view of the sharp change in slope observed for the most dilute solutions, it seems unwise to accord these points much weight in evaluating a standard potential for general use in the practical determination of paH.

The nine buffer mixtures of approximately 0.01 μ yield, as the data of table 3 show, a mean of 0.3350 ± 0.0002 for $E^{0\prime} + E_j$. If the two chloroacetate buffers are omitted and only solutions with paH above 3 are included, the average of seven results is 0.3352 ± 0.0001 v. The three dotted lines of figure 2, extended to the axis of ordinates, meet at 0.3353. From all of these considerations, we choose 0.3352 ± 0.0002 as the value of $E^{0\prime} + E_j$ that appears most suitable for use with buffer solutions composed of weak monobasic acids and their sodium

TABLE 3

Calculation of $E^{0\prime} + E_j$ for cell II at 25°C. from E.M.F. measurements of buffer solutions

BUFFER SYSTEM	COMPONENT a	COMPONENT b	TEMPERATURE	E	pK	paH	$E^{0\prime} + E_j$ (18°C.)	$E^{0\prime} + E_j$ (25°C.)	REFERENCES
	molarity	*molarity*	°C.	*volts*			*volts*	*volts*	
(a) Acetic acid and (b) sodium acetate	0.00203	0.00203	18	0.6103	4.757	4.744	0.3363	0.3359	*E* (95)
	0.00406	0.00406		0.6093		4.731	0.3361	0.3357	p*K* (56, 57)
	0.00608	0.00608		0.6088		4.724	0.3360	0.3356	
	0.00811	0.00811		0.6084		4.718	0.3359	0.3355	
	0.01007	0.01007		0.6077		4.712	0.3356	0.3352	
	0.01	0.01	25	0.6139	4.756	4.714		0.3351	*E* (36)
	0.01*	0.01*		0.6097		4.644		0.3352	p*K* (56, 104)
	0.1	0.1		0.6101		4.645		0.3354	
	0.02	0.02	25	0.6131		4.696		0.3354	*E* (76)
	0.04	0.04		0.6119		4.675		0.3354	
	0.06	0.06		0.6111		4.662		0.3354	
	0.08	0.08		0.6106		4.651		0.3355	
	0.1	0.1		0.6102		4.645		0.3355	
	0.009	0.001	25	0.5636		3.851		0.3359	*E* (102)
	0.008	0.002		0.5811		4.152		0.3356	
	0.018	0.002		0.5614		3.818		0.3356	
	0.016	0.004		0.5799		4.135		0.3354	
	0.01160	0.004717		0.5921		4.340		0.3354	
	0.01115	0.006181		0.5994		4.468		0.3352	
	0.01055	0.007594		0.6056		4.576		0.3350	
	0.01008	0.009134		0.6113		4.672		0.3350	
	0.01	0.01		0.6140		4.714		0.3352	
	0.01015	0.01278		0.6195		4.807		0.3352	

(a) Chloroacetic acid and (b) sodium chloroacetate	0.001072	0.0019	25	0.5176	2.855	3.077		0.3356	E	(102)
	0.006716	0.005108		0.4946		2.696		0.3352	pK	(134, 144)
	0.00784	0.00739		0.4995		2.785		0.3348		
	0.00868	0.01143		0.5075		2.924		0.3346		
	0.01169	0.01647		0.5084		2.944		0.3343		
	0.01443	0.01840		0.5056		2.900		0.3341		
	0.01006	0.01006	18	0.5031	2.836	2.912	0.3349	0.3345	E pK	(96) (134, 144, 164)
(a) Glycolic acid, (a) lithium chloride, and (b) lithium glycolate	0.01	0.01	25	0.5587	3.831	3.786		0.3348	E	(76)
	0.02	0.02		0.5564		3.761		0.3340	pK	(116)
(a) Glycolic acid and (b) sodium glycolate	0.01009	0.01009	18	0.5552	3.837	3.807	0.3354	0.3350	E pK	(96) (116)
(a) Lactic acid and (b) sodium lactate, in 0.0118 M NaCl	0.01	0.0094	18	0.5541	3.863	3.790	0.3353	0.3349	E pK	(96) (117)
(a) Formic acid and (b) sodium formate	0.005	0.005	18	0.5519	3.754	3.756	0.3351	0.3347	E pK	(95) (60)
(a) Propionic acid and (b) sodium propionate	0.0102	0.0102	18	0.6146	4.874	4.830	0.3357	0.3353	E pK	(95) (59)
(a) n-Butyric acid and (b) sodium n-butyrate	0.01066	0.01	18	0.6095	4.809	4.739	0.3358	0.3354	E pK	(95) (67)

TABLE 3—*Concluded*

BUFFER SYSTEM	COMPONENT a	COMPONENT b	TEMPERATURE	E	pK	paH	$E^{0\prime} + E_j$ (18°C.)	$E^{0\prime} + E_j$ (25°C.)	REFERENCES
	molarity	*molarity*	°C.	*volts*			*volts*	*volts*	
(a) Potassium dihydrogen phosphate and (b) disodium hydrogen phosphate	0.005	0.005	25	0.7508		7.018		0.3358	E (76)
	0.01	0.01		0.7471		6.959		0.3355	paH (8)
	0.015	0.015		0.7446		6.919		0.3354	
	0.02	0.02		0.7426		6.886		0.3354	
	0.025	0.025		0.7409		6.860		0.3352	
	0.0025†	0.0025	25	0.7534		7.050		0.3365	E (36)
	0.025†	0.025		0.7386		6.833		0.3345	paH (8)
	0.05†	0.05		0.7325		6.741		0.3338	
Borax	0.01		25	0.8781		9.177		0.3354	E (76)
	0.02			0.8774		9.173		0.3349	paH (109)
	0.03			0.8775		9.176		0.3348	
	0.04			0.8778		9.185		0.3346	
	0.05			0.8783		9.196		0.3344	

* In 0.09 M potassium chloride.

† NaH_2PO_4 instead of KH_2PO_4. These solutions also contained sodium chloride at a concentration equal to 0.97 × the molarity of each phosphate.

salts. The corresponding potential for the cell with a saturated calomel electrode (cell IV) is 0.2440 v.[8] For the molar scale of activity, $E^{0'} + E_j$ becomes 0.2439. This value is in good agreement with 0.2441, selected by Hitchcock and Taylor (76).

It is impossible to state what effect a change in the valence type of the buffer system will have upon $E^{0'} + E_j$ and, hence, how generally applicable this standard potential may be in determining the paH of buffered solutions of different and even unknown compositions. If measurements of hydrogen-calomel cells with dilute phosphate buffers were available, it is safe to say that they would furnish a standard potential greater than 0.3360 at an ionic strength of 0.01. The single measurement of Guggenheim and Schindler (36) in the dilute range gives 0.3365. The values of $E^{0'} + E_j$ computed from E.M.F. data (76) for phosphates at higher ionic strengths, together with the paH derived from measurements of cells without junction, are consistent with the results for monobasic acid systems, as shown in table 3. It is entirely possible that the change in slope that occurs at about 0.01 μ with acetate and chloroacetate buffer systems becomes apparent at a higher concentration when bivalent anions are present.

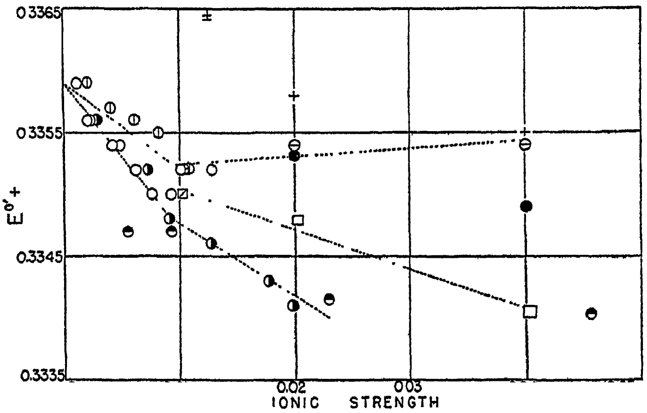

FIG. 2. $E^{0'} + E_j$ for cell II as a function of ionic strength at 25°C. Acetates: ⊖ (36, 76), ⦶ (95), ○ (102). Chloroacetates: ◑ (102). Formates: ◓ (95). Glycolates: □ (76), ▨ (96). Borates: ● (76). Phosphates: + (76), ± (36).

Nevertheless, the conclusion that the residual liquid-junction potentials (compare equation 9) may amount to 0.01 to 0.02 paH unit (0.6 to 1.2 mv.) is inescapable. It is clearly impossible to determine the paH of a solution that is "unknown" in every sense of the word with an uncertainty less than ±0.02 unit.

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[8] Although the presence of air alters the potentials of calomel and silver-silver halide electrodes in acid solutions, its effect upon only the silver-silver iodide electrode is significant in neutral halide solutions (128, 147, 158).

D. Determination of the paH of reference solutions

The potential of the saturated calomel electrode is not considered highly reproducible, and the use of this electrode as a standard cannot be recommended (113). Some possible causes of erratic behavior are hysteresis (163) and variations in the grain size of the calomel (162). Hence, one cannot expect always to make use of standard values of $E^{0'} + E_j$ such as are given in the foregoing section. For this reason it is always desirable to redetermine $E^{0'} + E_j$, that is, to standardize the cell, at frequent intervals by measurement of the electromotive force for a solution of known paH. The true standard potential is then unimportant, so long as the calibration remains unchanged.

Nevertheless, electromotive-force measurements of cells of types II and IV in different laboratories agree satisfactorily when the cell solutions are either buffered electrolytes or strong acid–salt mixtures, as a comparison of published data will testify (18, 36, 76, 102). Different choices of $E^{0'}$ or $E^{0'} + E_j$ are chiefly responsible for the lack of agreement on the paH values to be assigned to standard solutions. It is apparent from figure 2 that the choice of 0.3358 by MacInnes, Belcher, and Shedlovsky (102) resulted from the use of experimental data for very dilute buffer solutions. On the other hand, Hitchcock and Taylor obtained 0.3353 by the extrapolation of values obtained at ionic strengths in excess of 0.01. A difference of 0.008 in the paH values computed from the same measured electromotive force is the direct result of this difference of 0.5 mv. in $E^{0'} + E_j$. Except for the dilute acetate buffer, 0.01 *M* acetic acid and 0.01 *M* sodium acetate,[9] paH on the scale of Guggenheim and Schindler (36) appears improbably high, because their standard potential is too low.

Our choice of 0.3352 for $E^{0'} + E_j$ rests upon the two following considerations: (*a*) There is no theoretical explanation for an abrupt change below 0.01 μ in the slope of the plot of "apparent" paH with respect to ionic strength. We are therefore led to suspect an abnormal change of liquid-junction potential as the solute on one side of the boundary becomes attenuated. (*b*) It is quite improbable that the paH of the standard 0.01 *M* acetate buffer computed from measurements of cells without liquid junction is in error by more than ±0.005 unit. This value is 4.714. If $E^{0'} + E_j$ is 0.3352, the paH computed from the electromotive force of the cell with liquid junction is also 4.714. If the higher value, 0.3358, is chosen for the standard potential, however, the paH of this solution is found to be 4.704.

The reference solution that appears to have found most extensive use (18, 79, 90, 94, 153) is the mixture of 0.01 *M* hydrochloric acid and 0.09 *M* potassium chloride, often known as "Veibel's solution" (162). Inasmuch as the potential at the boundary of a strong acid mixture such as this and saturated potassium chloride differs somewhat from the potential between a buffer solution and the same bridge solution, this mixture is not to be recommended as a standard for general use.

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[9] Guggenheim and Schindler have apparently made an error in calculating the paH of this buffer solution. The paH value should read 4.71 instead of 4.80 on pages 535 and 538 of their paper (36).

Table 4 illustrates the essential agreement among paH values of buffered solutions computed from the data of Hitchcock and Taylor (H & T) (76) and MacInnes, Belcher, and Shedlovsky (M, B, & S) (102) and those values derived from measurements of cells without liquid junction. The paH in the second and third columns is based upon standard potentials of 0.2440 for cell IV and 0.3352 for cell II. At present it is impossible to say definitely what effect the presence of salts of the higher valence types may have upon the standard potential. Nevertheless, paH values for phosphate buffer solutions have been included in the table for purposes of comparison. Methods by which the paH can be calculated from the electromotive force of cells without liquid junction will be considered in the following section.

TABLE 4

paH of standard buffer solutions at 25°C.

($E^{0'} + E_j = 0.3352$)

SOLUTION	paH (H & T)	paH (M, B, & S)	paH (FROM CELLS WITHOUT LIQUID JUNCTION)	REFERENCE (CELLS WITHOUT LIQUID JUNCTION)
Acid potassium phthalate (0.05 *M*)	4.010	4.010	4.005	(50)
Acetic acid (0.01 *M*) and sodium acetate (0.01 *M*)	4.716	4.710	4.714	This paper
Acetic acid (0.1 *M*) and sodium acetate (0.1 *M*)	4.650	4.650	4.65 ±0.01	This paper
Potassium dihydrogen phosphate (0.01 *M*) and disodium hydrogen phosphate (0.01 *M*)	6.965		6.959	(8)
Potassium dihydrogen phosphate (0.025 *M*) and disodium hydrogen phosphate (0.025 *M*)	6.860		6.860	(8)
Borax (0.01 *M*)	9.180		9.177	(109)

VII. THE PAH OF BUFFER SOLUTIONS FROM MEASUREMENTS OF CELLS WITHOUT LIQUID JUNCTION

As indicated in an earlier section, a cell without liquid junction and the pwH scale should be used for determinations of acidity whenever it is possible to do so. The great majority of approximate measurements, however, are made of cells with liquid junction, and the paH scale appears the most suitable for interpreting these results. In view of the relative ease with which accurate E.M.F. measurements of cells without liquid junction can be made over a wide range of temperatures, an effort has been made to use these cells for establishing paH standards with which to calibrate the pH meter and other cells with liquid junction. The assumptions on which these methods are based will be discussed. Inasmuch as the paH definition (equation 5) is used throughout, all of these methods of calculation are equivalent in dilute solutions. An attempt will be made to determine the limiting value of the ionic strength below which these different assumptions will yield substantially identical paH values.

A. Electromotive force and pwH

In order to make a comparison with the measurements of cells with liquid junction reported by Hitchcock and Taylor (76, 77) and MacInnes, Belcher, and Shedlovsky (102), some studies of the buffer solutions used by these investigators were undertaken with the use of cells without liquid junction (3). The cells were of type III. In general, the electromotive force was obtained at 0°, 25°, 38°, and 50°C. The value at 0°C. was found by linear extrapolation with the use of the E.M.F. measured at temperatures of 25°C. and a few tenths of a degree above 0°C.

In addition to the buffer solutions studied by Hitchcock and Taylor, cell measurements were made with 0.02 *m* solutions of potassium dihydrogen citrate and potassium tetroxalate. Potassium bitartrate and potassium tetroxalate separated from the 0.03 *m* and 0.1 *m* solutions when these were cooled, so measurements at 0°C. could not be obtained. Molalities were used throughout, but the difference of pH between the weight and volume scales of concentration is less than 0.001 unit and therefore unimportant, so long as the same standard state is employed. Two concentrations of sodium chloride, 0.01 *m* and 0.005 *m*, were utilized, in order that pwH in the absence of chloride could be obtained by a short extrapolation. These data are summarized in table 5.

The pwH numbers for these buffer solutions are given in table 6, together with those of several other useful buffer solutions that have been studied by measurements of cells of type III. The data for 0.1 *m* hydrochloric acid and mixtures of 0.01 *m* hydrochloric acid with 0.09 *m* sodium and potassium chlorides are included. The pwH values for these were computed from the mean activity coefficient of hydrochloric acid in the mixtures (53). For the other solutions, equation 16 was used. The ionic strengths were obtained, by arithmetical approximations, with the aid of the first dissociation constant of oxalic acid (19) and the first and second constants of tartaric (19) and citric acids (18).

B. Evaluation of ionic activity coefficients

It is evident from the mass law that

$$-\log\,(f_{\mathrm{H}}f_{\mathrm{Cl}}m_{\mathrm{H}}) = \mathrm{p}K - \log\frac{m_{\mathrm{HA}}}{m_{\mathrm{A}}} - \log\frac{f_{\mathrm{HA}}f_{\mathrm{Cl}}}{f_{\mathrm{A}}} \qquad (28)$$

in which HA is an uncharged weak acid or an acid anion, and A is the anion with one more negative charge than HA. The last term of this equation will be called $\log f_r$. Expressions for paH are derived by adding $\log f_{\mathrm{Cl}}$ to either side of equation 28:

$$\mathrm{paH} = -\log\,(f_{\mathrm{H}}f_{\mathrm{Cl}}m_{\mathrm{H}}) + \log f_{\mathrm{Cl}} \qquad (29)$$

and

$$\mathrm{paH} = \mathrm{p}K - \log \frac{m_{\mathrm{HA}}}{m_{\mathrm{A}}} - \log \frac{f_{\mathrm{HA}} f_{\mathrm{Cl}}}{f_{\mathrm{A}}} + \log f_{\mathrm{Cl}} \tag{29a}$$

In equation 28, both of the terms that contain activity coefficients are physically defined.[10] This significance is lacking, however, in the expressions for paH. To compute $-\log a_{\mathrm{H}}$, a numerical value must be assigned to f_{Cl}. An arbitrary assumption must be introduced at this point, for neither f_{Cl} nor $f_{\mathrm{HA}}/f_{\mathrm{A}}$ can be evaluated by thermodynamic methods. This assumption should appear reasonable in the light of the modern theory of electrolytes.

TABLE 5

Electromotive force of the cell: H_2; *buffer solution,* NaCl, AgCl; Ag *at 0°, 25°, 38°, and 50°C.*

BUFFER SOLUTION	NaCl	E_0	E_{25}	E_{38}	E_{50}
	molality				
0.1 *m* potassium tetroxalate	0.01		0.43742	0.43895	0.44001
	0.005		0.45491	0.45699	0.45889
0.02 *m* potassium tetroxalate	0.01	0.45329	0.45978	0.46197	0.46342
	0.005	0.46945	0.47736	0.48031	0.48250
0.03 *m* potassium bitartrate	0.01		0.55565	0.56085	0.56585
	0.005		0.57372	0.57965	0.58528
0.1 *m* potassium dihydrogen citrate	0.01	0.55691	0.56695	0.57195	0.57638
	0.005	0.57352	0.58480	0.59058	0.59614
0.02 *m* potassium dihydrogen citrate	0.01	0.56000	0.57052	0.57575	0.58058
	0.005	0.57671	0.58870	0.59475	0.60027
0.1 *m* acetic acid + 0.1 *m* sodium acetate	0.01	0.60464	0.62242	0.63153	0.63982
	0.005	0.62082	0.64017	0.65000	0.65897
0.01 *m* acetic acid + 0.01 *m* sodium acetate	0.01	0.60436	0.62230	0.63145	0.63982
	0.005	0.62062	0.64013	0.65003	0.65905

The theories of electrolytic solutions offer some guidance in splitting the activity-coefficient terms of equation 28, but their aid is limited in general to dilute solutions. In solutions so dilute that the limiting law of Debye and Hückel is obeyed, the validity of equation 13 can safely be assumed. The limiting law indicates further that the logarithms of ionic activity coefficients are proportional to the squares of the charges on the ions. The Debye–Hückel equations and their extended forms have been conspicuously successful in repre-

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[10] If f_{H} is written in both numerator and denominator, it is evident that $\log (f_{\mathrm{HA}} f_{\mathrm{Cl}}/f_{\mathrm{A}})$ is $2 \log (f_{\mathrm{HCl}}/f_{\mathrm{HA}})$, where f_{HCl} and f_{HA} are, respectively, the mean activity coefficients of hydrochloric acid and of a monobasic weak acid, HA.

TABLE 6

pwH at 0°, 25°, 38°, and 50°C.

SOLUTION	SODIUM CHLORIDE	IONIC STRENGTH	pwH = $-\log (f_H f_{Cl} m_H)$ AT				REFERENCE
			0°C.	25°C.	38°C.	50°C.	
	molality						
0.1 *m* hydrochloric acid		0.1	1.190	1.198	1.204	1.212	(58)
0.1 *m* potassium tetroxalate	0.01			1.636	1.653	1.677	
	0.005			1.631	1.644	1.670	
	0.000	0.144		1.626	1.635	1.663	
0.02 *m* potassium tetroxalate	0.01		2.002	2.014	2.025	2.042	
	0.005		2.000	2.010	2.022	2.039	
	0.000	0.034	1.998	2.006	2.019	2.036	
0.01 *m* hydrochloric acid + 0.09 *m* sodium chloride		0.1	2.200	2.206	2.211		(53)
0.01 *m* hydrochloric acid + 0.09 *m* potassium chloride		0.1	2.203	2.208	2.212		(53)
0.03 *m* potassium bitartrate	0.01			3.635	3.628	3.640	
	0.005			3.640	3.631	3.642	
	0.000	0.035		3.645	3.634	3.644	
0.1 *m* potassium dihydrogen citrate	0.01		3.915	3.826	3.808	3.804	
	0.005		3.920	3.827	3.808	3.812	
	0.000	0.113	3.925	3.828	3.808	3.820	
0.02 *m* potassium dihydrogen citrate	0.01		3.972	3.887	3.869	3.870	
	0.005		3.979	3.893	3.876	3.876	
	0.000	0.023	3.986	3.899	3.883	3.882	
0.05 *m* acid potassium phthalate	0.01		4.085	4.090	4.113	4.152	(45)
	0.005		4.087	4.091	4.117	4.155	
	0.000	0.053	4.089	4.092	4.121	4.158	
0.1 *m* acetic acid + 0.1 *m* sodium acetate	0.01		4.796	4.764	4.773	4.794	
	0.005		4.793	4.763	4.771	4.792	
	0.000	0.1	4.790	4.762	4.769	4.790	
0.01 *m* acetic acid + 0.01 *m* sodium acetate	0.01		4.791	4.762	4.771	4.794	
	0.005		4.790	4.762	4.771	4.793	
	0.000	0.01	4.789	4.762	4.771	4.792	
0.025 *m* potassium dihydrogen phosphate + 0.025 *m* disodium hydrogen phosphate	0.01		7.081	6.962	6.941	6.939	(8)
	0.005		7.085	6.966	6.946	6.945	
	0.000	0.1	7.089	6.970	6.951	6.951	

TABLE 6—*Concluded*

SOLUTION	SODIUM CHLORIDE	IONIC STRENGTH	$pwH = -\log (f_H f_{Cl} m_H)$ AT				REFERENCE
			0°C.	25°C.	38°C.	50°C.	
	molality						
0.01 *m* potassium dihydrogen phosphate + 0.01 *m* disodium hydrogen phosphate	0.01		7.139	7.021	7.000	6.999	(8)
	0.005		7.148	7.029	7.009	7.008	
	0.000	0.04	7.157	7.037	7.018	7.017	
0.05 *m* sodium tetraborate (borax)	0.01	0.11	9.614	9.303	9.195	9.120	(109)
0.01 *m* sodium tetraborate (borax)	0.01	0.03	9.517	9.242	9.466	9.083	(109)

senting the mean activity coefficients of strong electrolytes at intermediate and even high concentrations. No extension of equation 13 is forthcoming, however, nor is any information to be derived from these equations regarding the upper limit of validity of the relationship between the activity coefficients of ions of single and double charge.

In figure 3, the common logarithms of the ratios of the mean activity coefficients of eighteen uni-univalent strong electrolytes to that of hydrochloric acid are plotted as a function of ionic strength. The activity coefficients of the formates were taken from the papers of Guggenheim (35) and those of the other electrolytes from tables given in the monograph of Harned and Owen (64). The logarithms of the ratios of the mean activity coefficients of eight strong electrolytes of the 2–1 and 1–2 valence types to the square of the mean activity coefficient of hydrochloric acid are plotted in figure 4 as a function of ionic strength. Broken lines are drawn when the ratio is known only at an ionic strength of 0.3.

It is evident in figures 3 and 4 that the valence relations of the limiting law for mean activity coefficients hold fairly well in a part of the range where specific effects render the simple limiting equation useless. Although no appreciable individual differences among the mean activity coefficients of many uni-univalent electrolytes are apparent somewhat above the so-called "Debye–Hückel range," it is doubtful that equation 13 can be more than approximately true at higher ionic strengths (36, 161). Kortüm (92), however, believes that the general form of equation 13 for an ion i of charge z_i in an electrolyte which dissociates completely into ν_+ cations and ν_- anions of valences z_+ and z_-, respectively,

$$\ln f_i = \frac{\nu z_i^2}{\nu_+ z_+^2 + \nu_- z_-^2} \ln f_\pm \tag{30}$$

where $\nu = \nu_+ + \nu_-$, is valid for all electrolytes up to an ionic strength of 0.01, and for potassium chloride to 0.1.

Probably the most fruitful expositions of ionic behavior have been made by

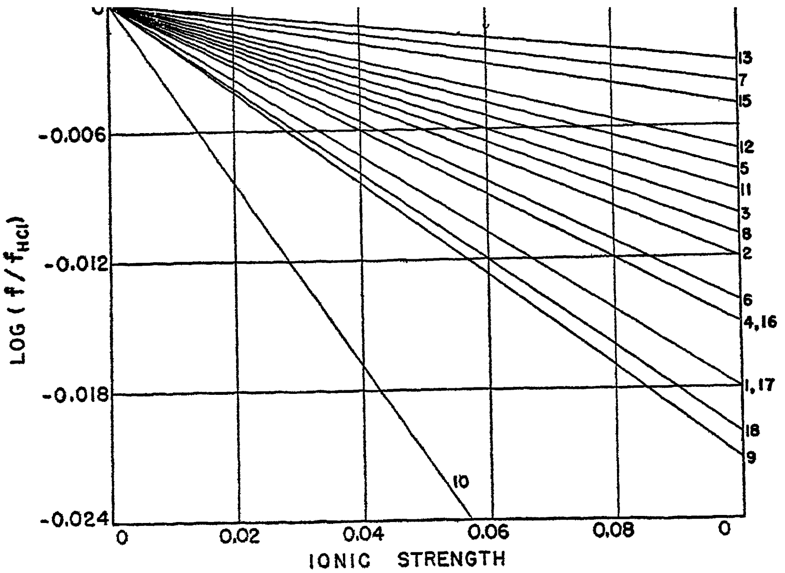

FIG. 3. Logarithms of the ratios of mean activity coefficients of strong uni-univalent electrolytes to the mean activity coefficient of hydrochloric acid plotted as a function of ionic strength. Odd numbers indicate sodium salts and even numbers potassium salts. 1, 2—fluorides; 3, 4—chlorides; 5, 6—bromides; 7, 8—iodides; 9, 10—nitrates; 11, 12—formates; 13, 14—acetates; 15, 16—thiocyanates; 17, 18—toluenesulfonates.

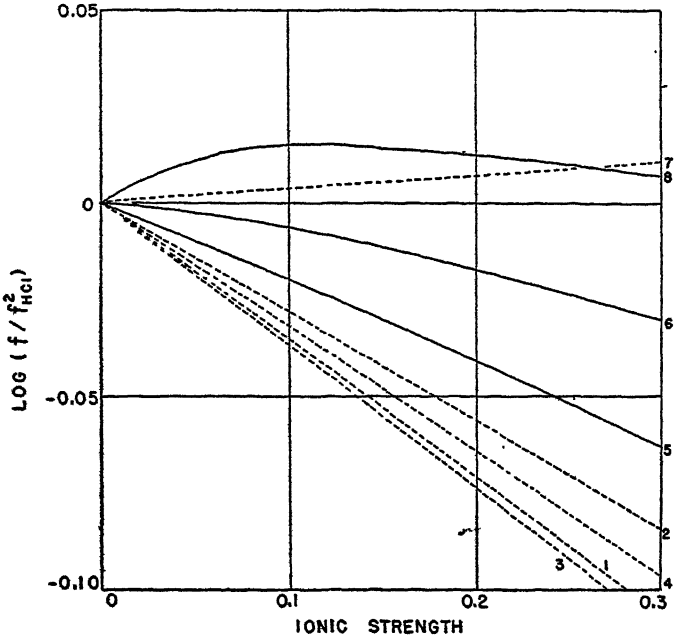

FIG. 4. Logarithms of the ratios of mean activity coefficients of strong electrolytes of the 1–2 and 2–1 valence types to the square of the mean activity coefficient of hydrochloric acid plotted as a function of ionic strength. 1, sodium sulfate (62); 2, lithium sulfate (133); 3, potassium sulfate (133); 4, sodium thiosulfate (133); 5, barium chloride (142, 160); 6, calcium chloride (146); 7, magnesium bromide (132); 8, zinc iodide (4).

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I. INTRODUCTION

Interest in the analytical chemistry of thorium has been extremely sporadic. The extensive use of thorium compounds in the incandescent mantle lamp industry prompted much exploratory work in thorium chemistry and in the development of analytical methods for the element during the latter part of the nineteenth century and the early part of the twentieth. However, decline in the use of such mantles in recent years has been paralleled by a general decline in interest in the characteristics of thorium as such. Recent observations upon the importance of the thorium nucleus in fission studies have again focussed attention upon the element, and it is apparent that much is still to be learned about the behavior of the element and its compounds. Because of the importance of the analytical properties of thorium in any studies relating to its chemistry, a detailed summary and critical review of available information seem apropos. Although a number of phases of the analytical chemistry of thorium have been treated previously (10a, 24, 38, 54, 89, 90, 91, 120, 134, 183, 231), no concise account embracing the entire subject is available.

The paucity of really characteristic reactions of thorium and its compounds and the marked similarities between the chemistry of thorium and that of almost every other element associated with it in nature complicate its analytical chemistry. Since but a single oxidation state (+4) is recognized, no reactions dependent upon change in oxidation state are possible. Furthermore, since the thorium ion is colorless and yields but few colored derivatives, distinctive reactions are rare.

Interferences produced by zirconium[1] and hafnium compounds[1] are in general less complex and less important than those produced by scandium, yttrium, and rare earth metal compounds. Separation of thorium from these materials is complicated by extreme similarities in compound solubilities and stabilities.

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[1] Because of the extreme similarities between zirconium and hafnium compounds and because most of the zirconium materials used in the investigations described herein undoubtedly contained hafnium compounds as well, the term zirconium, whenever used, may be taken to mean either the pure material or its admixture with hafnium.

THE ANALYTICAL ASPECTS OF THORIUM CHEMISTRY

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reasonable, for the several plausible assumptions upon which the calculation of the single-ion activity coefficients is based are then substantially equivalent. At higher concentrations, appreciable differences among these several paH scales appear. As yet, only the pwH ($-\log a_H f_i$) retains its significance at all ionic strengths, and this unit is of limited usefulness in the practical determination of acidity.

The computation of paH from the electromotive force of cells without liquid junction in dilute solutions is valid for strong acids and mixtures of strong electrolytes as well as for buffered solutions over the entire pH range. For this reason, paH derived in this way is useful in the standardization of cells with liquid junction.

In view of the multiplicity of pH scales in use at the present time, all published pH values should be accompanied by a statement of the type of cell measured, of the standard potential used in computing the results, and of whether any attempt was made to eliminate the liquid-junction potential or to correct the electromotive force therefor. When the pH meter is employed, the pH values of the standard reference solutions with which the instrument was calibrated should be specified.

The pH can never possess the absolute significance of a true thermodynamic constant. It is therefore of primary importance that a single unequivocal definition of the pH scale be generally recognized. That the definition will perforce be stated in terms of operations and calculations is of secondary concern.

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those of Harned and Ehlers at each temperature. The molar and molal scales of concentration can be used interchangeably, in this range of concentration, without sensible error.

The several paH scales that have been discussed here are essentially equivalent at ionic strengths as low as 0.01. The equations that define p_3H, p_4H, and p_5H are inapplicable to buffers of the monobasic acid type, however, and the practical disadvantage of buffers of other types at such a low ionic strength is well recognized. A series of solutions of known paH but of different ionic character or composition need not necessarily yield a uniform calibration of a cell with liquid junction over a wide range of pH. In this respect, buffers of the type: 0.01 *M* HA, 0.01 *M* NaA, seem well suited for purposes of standardization. At this low ionic strength, the paH can be said to possess some measure of thermodynamic meaning.

Primary standards such as these can be used to redetermine the value of $E^{0'} + E_j$ in equation 11 and, with the aid of cells of type II or IV, the paH values of the many convenient secondary standards of somewhat higher concentrations and varying types. The computation of hydrogen-ion activity at high or even moderate ionic strengths is quite uncertain and probably will remain so.

IX. SUMMARY

Unfortunately, the pH computed from the electromotive force of cells can only be defined as a unit on an arbitrary scale. Until the character of the ionic activity coefficient is precisely defined, the residual liquid-junction potential will remain indeterminate. Definitions of pH therefore rest upon arbitrary assumptions that enable the liquid-junction potential to be evaluated or eliminated or that permit the activity coefficient of a single ionic species to be derived from measurable combinations of activity coefficients.

In itself, the concentration of hydrogen ion is a very suitable measure of acidity. Activity coefficients appear in the equations for electromotive force, however, and pcH is not readily obtained from measurements of galvanic cells. By choice of different values for $E^{0'} + E_j$ in the equation

$$\text{pH} = \frac{E - (E^{0'} + E_j)}{k} \tag{54}$$

a family of pH scales can be defined. When $E^{0'} + E_j$ is taken to be 0.3376 at 25°C. for the cell with hydrogen and 0.1 *N* calomel electrodes (cell II), the conventional scale defined by Sørensen (psH scale) results. The psH unit is satisfactory for reproducible comparisons of the work of different investigators, but it has no meaning in terms of chemical equilibria. Assignment of 0.3352 to $E^{0'} + E_j$ defines a unit that corresponds closely to $-\log a_H$, insofar as it can be estimated, in the thermodynamic equilibria for a number of weak monobasic acids. The general adoption of this activity scale and the paH unit seems warranted.

Measurement of the electromotive force of cells without liquid junction furnishes a means of calculating the paH of buffer mixtures composed of weak acids and their salts. At ionic strengths of 0.01 or below, these values are quite

HA and 0.01 m NaA, where HA is a weak monobasic acid, is then arbitrarily set equal to the average of $-\log f^0_{\mathrm{HCl}}$ and $-\log f_{\mathrm{NaCl}}$ in a 0.01 m solution of sodium chloride. At 0° and 40°C., these two quantities differ by 0.0020 and 0.0011, respectively. The values of $-\log f^0_{\mathrm{Cl}}$ obtained in this manner are given by

$$-\log f^0_{\mathrm{Cl}} = 0.0436 + 0.00004t \tag{52}$$

where t, the temperature in degrees Centigrade, lies between 0 and 40. At 0°, 25°, and 38°C., $-\log f^0_{\mathrm{Cl}}$ is respectively 0.0436, 0.0446, and 0.0451. The paH value at 0.01 μ defined in this way is given by

$$\mathrm{paH} \equiv -\log (f_{\mathrm{H}} f_{\mathrm{Cl}} m_{\mathrm{H}})^0 - 0.0436 - 0.00004t \tag{53}$$

The paH of the reference acetate buffer is computed from equation 29a with the aid of this defined value of $-\log f^0_{\mathrm{Cl}}$. At ionic strengths below 0.1, log $(f_{\mathrm{HAc}} f_{\mathrm{Cl}} / f_{\mathrm{Ac}}) = -0.06\ \mu$ (56). Values of this quantity for formate, propionate, and borate buffer solutions are to be found in the literature (59, 60, 107, 119). The buffer ratio is determined by arithmetical approximations. The paH of four buffers computed by equations 29a and 52 at 0°, 25°, and 38°C. is given in table 14.

TABLE 14

paH of buffer solutions composed of 0.01 M HA *and 0.01 M* NaA *at 0°, 25°, and 38°C.*

A	paH AT		
	0°C.	25°C.	38°C.
Formate	3.760	3.727	3.737
Acetate	4.741 4.745*	4.714 4.717*	4.724 4.726*
Propionate	4.853	4.831	4.844
Borate†	9.466	9.190	9.093

* Computed by equation 53 from $-\log (f_{\mathrm{H}} f_{\mathrm{Cl}} m_{\mathrm{H}})^0$ given in table 6.

† 0.005 M borax.

In only five instances can this paH be compared with paH derived from the cell with liquid junction. Hitchcock and Taylor (76) found 4.714 for the acetate buffer at 25°C., whereas MacInnes, Belcher, and Shedlovsky (102) give 4.700 for this temperature and 4.710 at 38°C. The corrected value[9] of Guggenheim and Schindler (36) for this solution is 4.713 at 25°C. The paH at 38°C. computed from the data of Hitchcock and Taylor (77) for the borax buffer, 9.093, is identical with that given in table 14.

The electromotive-force measurements given in table 5 for the 0.01 m acetate buffer are about 0.2 mv. higher than the data of Harned and Ehlers (56, 57). The paH of this buffer computed from equation 53 and listed in table 13 is accordingly 0.003 unit higher than that calculated by equations 29a and 52. The measurements of the 0.1 m acetate buffer are, however, in excellent agreement with

C. paH of the reference buffer

A determination of the paH of the reference buffer solution, for example, a mixture of acetic acid and sodium acetate, requires the evaluation of log f_{Cl} in equation 29 or 29a. This can be done only by introducing an assumption. One of the most plausible, perhaps, is to assume that the activity coefficient of chloride ion in the reference buffer (with sodium chloride or in its absence) is equal to the mean activity coefficient of hydrochloric acid in a mixture of similar composition and identical ionic strength. Such an assertion is probably justifiable at an ionic strength of 0.01 or below (92, 97, 155). The value of log f_{Cl} in 0.01 *m* hydrochloric acid derived by Scatchard (136) and that computed by the MacInnes assumption (99) differ from the logarithm of the mean activity coefficient by only 0.002 or less. The buffers of known paH are restricted to this low range of ionic strengths, although accurate differences of paH may possibly be obtainable at somewhat higher concentrations.

The estimation of log f^0_{Cl} in 0.01 *m* acetic acid, 0.01 *m* sodium acetate is accordingly made as follows. In a 0.01 *m* solution of pure hydrochloric acid, $-\log f_{\mathrm{HCl}}$ is 0.0434 (58, 128, 145). The medium effect of 0.01 *m* acetic acid can be estimated from the measurements of Owen (118) to be considerably less than 0.001.[14] The concentration of hydrochloric acid, however, is zero in the reference buffer, and the molality of sodium ion is 0.01. The effect of sodium ions can be estimated from the data for mixtures of hydrochloric acid and sodium chloride. The electromotive-force data of Harned (53) permit a calculation of the change in activity coefficient at 0–40°C. produced by adding sodium chloride to hydrochloric acid at low ionic strengths. The value of $-\log f_{\mathrm{HCl}}$ at 25°C. is increased by the following amounts when 0.01 mole of sodium chloride is substituted for 0.01 mole of hydrochloric acid: 0.0004 at an ionic strength of 0.06, 0.0008 at 0.03, and 0.0011 at 0.02. By extrapolation to an ionic strength of 0.01, $-\log f_{\mathrm{HCl}}$ is found to be higher in 0.01 *m* sodium chloride by 0.0014 than in 0.01 *m* hydrochloric acid, that is, 0.0448. In the same way, $-\log f_{\mathrm{HCl}}$ in 0.01 *m* sodium chloride is found to be 0.0446 at 0°C. and 0.0459 at 40°C. The extrapolations were made on plots of these calculated differences as a function of the square root of the ionic strength.

The activity coefficient of chloride ion could be identified with the mean activity coefficient of sodium chloride in its pure 0.01 *m* solution with equal justification. From the measurements of Brown and MacInnes (24), $-\log f_{\mathrm{NaCl}}$ is 0.0441. The medium effect appears to be larger with sodium chloride than with hydrochloric acid (1) but can again be neglected when the concentration of non-electrolyte is 0.01 *m*. The mean activity coefficient of sodium chloride at other temperatures was calculated from its value at 25°C. with the aid of the relative partial molal heat content of sodium chloride from the measurements of Gulbransen and Robinson (37).

The activity coefficient of chloride ion in a buffer of the composition 0.01 *m* among a series of buffer solutions of ionic strengths sufficiently high as to be experimentally accessible. The electromotive force, E, of the concentration cell,

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[14] Dioxane in the same concentration would produce a change of about 0.001 (64), and the effect of methanol would be entirely negligible (1).

H_2; reference buffer, NaCl, AgCl; Ag–Ag; AgCl, buffer, NaCl; H_2 Cell XII

when the molality of chloride is the same throughout, is given by

$$E/k = \text{paH}' - \text{paH}'' - \log (f'_{\text{Cl}}/f''_{\text{Cl}}) \tag{50}$$

where the single primes refer to the reference solution and the double primes to the buffer on the right of cell XII. The compositions of the buffer solutions would necessarily be so carefully matched that the last term of equation 50 could be assumed to be smaller than the desired accuracy of the difference of paH.

In terms of equation 29a, the difference of paH is given by

$$\text{paH}' - \text{paH}'' = \text{p}K' - \text{p}K'' - \log (m'_{\text{HA}}m''_{\text{A}}/m''_{\text{HA}}m'_{\text{A}})$$
$$-\log (f'_{\text{HA}}f''_{\text{A}}f'_{\text{Cl}}/f''_{\text{HA}}f'_{\text{A}}f''_{\text{Cl}}) + \log (f'_{\text{Cl}}/f''_{\text{Cl}}) \tag{51}$$

The next to the last term of equation 51 is evidently $\log f''_r - \log f'_r$. It can be obtained readily from measurements of the E.M.F. of cell XII either in the presence of sodium chloride or, by extrapolation, in its absence. The ratio of the activity coefficient of chloride ion in the two media cannot be evaluated. One can, however, ascertain the limit of the ionic strength above which the next to the last term of equation 51 exceeds the desired accuracy, for example 0.003 unit, of the difference in paH. When the ionic strength is well below this upper limit, $\log (f'_{\text{Cl}}/f''_{\text{Cl}})$, which is part of this measured activity-coefficient term, can probably be assumed to be smaller than 0.003 also. The difference between the paH of the two solutions is then obtained from equation 50 or 51.

With two notable exceptions, namely, carbonates and phenolsulfonates, the buffer solutions composed of primary and secondary sodium or potassium salts (figure 10) yield approximately equal activity-coefficient terms at ionic strengths below 0.02. The monobasic acid series has the same degree of uniformity below about 0.03 (figure 9). The ionic strength of an equimolal buffer of the first type is, however, four times the molality of each buffer salt when chloride is absent. Buffer solutions prepared from weak monobasic acids can readily be used at ionic strengths as low as 0.01.

It is not impossible, then, to define a series of paH standards that covers a considerable range of acidity with a high degree of internal consistency. A series of monobasic acid buffer solutions appears most suitable. The differences of pH between each buffer and a member of the series arbitrarily chosen as a reference would correspond closely to differences in $-\log a_{\text{H}}$. The ionic strength would necessarily be less than 0.03 and identical for each solution. The buffers would likewise be identical with respect to kind and concentration of cation and concentration of neutral molecules. The problem of assigning a paH value to the reference solution will be considered in the next section.

posed of chloride and the primary and secondary anions of dibasic or polybasic acids and $\log f_r$ for a reference mixture containing equal molalities of potassium dihydrogen phosphate, disodium hydrogen phosphate, and sodium chloride (8). The buffer ratio is unity unless otherwise stated. The activity coefficient of chloride ion in the reference mixture is again designated f'_{Cl}. Values of $\log f_r$ at each ionic strength were computed by equation 37 with the aid of a^* and β^* from the literature reference cited. The electromotive-force measurements of Harned and Scholes (66) at 25°C. were used to obtain $\log (f_{HCO_3}f_{Cl}/f_{CO_3})$ in mixtures of sodium bicarbonate, sodium carbonate, and sodium chloride. These values, fitted to equation 37, gave $a^* = 10.0$ and $\beta^* = 0.417$. Figures 9 and 10 reveal a greater uniformity, at intermediate ionic strengths, among the values of $\log f_r$ for systems of monobasic acids and their sodium and potassium salts than is found for systems that are composed of the primary and secondary sodium and potassium salts.

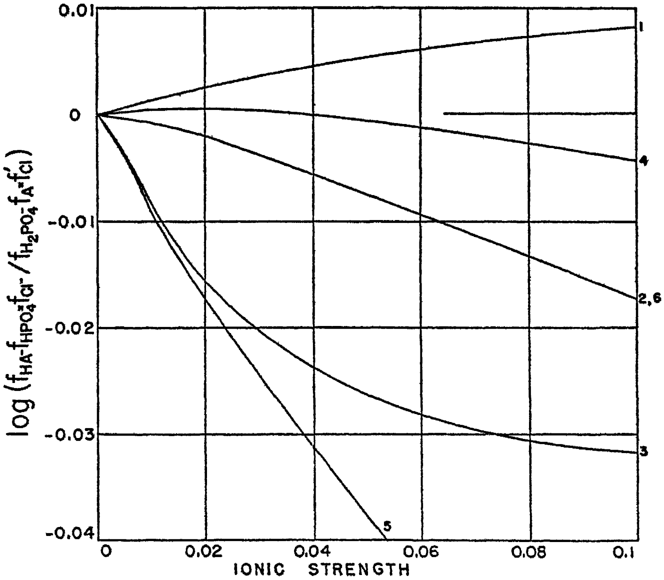

FIG. 10. Differences between $\log f_r$ for mixtures of chloride and primary and secondary anions of dibasic and polybasic acids and a reference buffer composed of equal molalities of potassium dihydrogen phosphate, disodium hydrogen phosphate, and sodium chloride plotted as a function of ionic strength. 1, phosphates, sodium salts (6); 2, malonates, sodium salts (48); 3, carbonates, sodium salts (66); 4, phthalates, potassium salts (47); 5, potassium *p*-phenolsulfonate, sodium hydroxide, sodium chloride (12); 6, potassium binoxalate, sodium oxalate, sodium chloride, 1:5:1 (125).

B. Differences of paH

The approximate equality of the activity coefficients of ions of like charge in the same medium suggests the possibility of determining differences of $-\log a_H$

A comparison of $\log f_r \equiv \log (f_{\mathrm{HA}} f_{\mathrm{Cl}}/f_{\mathrm{A}})$, where HA is a weak monobasic acid and A its univalent anion, for five buffer systems with $\log f_r$ for mixtures of acetic acid, sodium acetate, and sodium chloride (56, 57) is shown in figure 9. The term $\log (f_{\mathrm{HA}} f_{\mathrm{Ac}} f_{\mathrm{Cl}}/f_{\mathrm{HAc}} f_{\mathrm{A}} f'_{\mathrm{Cl}})$, where f'_{Cl} is the activity coefficient of chloride ion in the reference buffer of acetic acid (HAc) and sodium acetate, is plotted as a function of ionic strength. This activity-coefficient term is the difference between $\log f_r$ for the two buffer–chloride systems that are being compared. The data are taken from the literature and relate, in general, to mixtures in which the molality of chloride equals that of the weak acid and its salt. The cation in each buffer is sodium or potassium. It is apparent that the quantity plotted as ordinate is the logarithm of the product of three quantities, all of which should be approximately unity. These are the ratios of the activity coefficients of two neutral molecules,[13] of two different univalent anions, and of the same ion (chloride) in two different solutions of the same ionic strength.

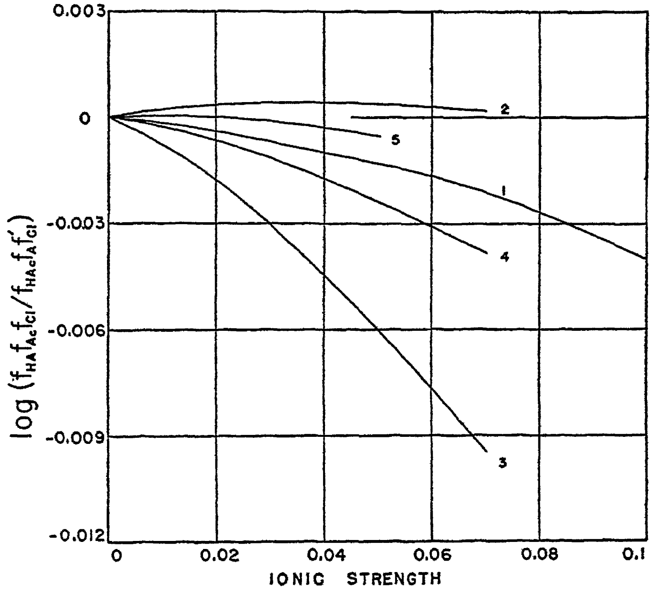

FIG. 9. Differences between $\log f_r$ for monobasic acid buffers with chloride and a reference buffer composed of equal molalities of acetic acid, sodium acetate, and sodium chloride plotted as a function of ionic strength. 1, formate, potassium salts (60); 2, propionate, sodium salts (59); 3, *n*-butyrate, sodium salts (67); 4, glycolate, potassium salts (116); 5, borate, sodium salts (107, 119).

Figure 10 is a similar plot of differences between $\log f_r$ for six mixtures com-

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[13] Randall and Failey (127) have compiled data on the activity coefficients of many neutral molecules in salt solutions. The ratio of the activity coefficients of two different neutral molecules in the same salt medium of moderate concentration is close to unity. The activity coefficient of acetic acid in sodium acetate is given by $\log f_{\mathrm{HAc}} = -0.014\ \mu$. In sodium chloride, on the contrary, f_{HAc} is greater than 1.

Electromotive-force measurements likewise furnish a comparison of activity coefficients in equimolal buffer mixtures of acetic acid and sodium acetate with added sodium chloride and potassium iodide. The data of Harned and Ehlers (56) for cell III at 25°C. show that log $(f_{HAc}f_{Cl}/f_{Ac})$ in acetate buffer solutions to which sodium chloride has been added in molality equal to that of each component of the buffer is given by $-0.06\ \mu$. Bates and Vosburgh (13) have measured the E.M.F. of the cell,

H_2; HAc (m_1), NaAc (m_1), KI (m_2), Hg_2I_2;Hg Cell X

at the same temperature. The ratio m_2/m_1 varied from 0.55 to 1.0 in the six buffer solutions studied. Their data show that log $(f_{HAc}f_I/f_{Ac})$ is $-0.14\ \mu$ in these mixtures. In this instance, the substitution of iodide for chloride evidently *decreases* the activity-coefficient term, in apparent contradiction of the change in log f_r^0 found for phosphate buffer solutions. It must be remembered, however, that the two acetate media differ with respect to the kind and concentration of the cations. An increase in the E.M.F. of cells of types III and IV when potassum ion replaces sodium ion is not an uncommon observation (6, 9, 18, 76, 77). The activity coefficient of hydriodic acid is greater than that of hydrochloric acid in the same cationic environment, and the substitution accordingly increases log f_r^0. On the other hand, these results indicate that the activity coefficient of hydriodic acid in an acetate–potassium iodide mixture is smaller than that of hydrochloric acid in an acetate–sodium chloride mixture of the same ionic strength. Unfortunately, the activity coefficient of hydriodic acid in salt solutions has not been measured. Nevertheless, this conclusion is entirely consistent with salt effects upon the activity coefficients of hydrochloric and hydrobromic acids (53, 64).

At ionic strengths below 0.05, the substitution of f_{Br} or f_I for f_{Cl} in the activity-coefficient term, log f_r^0, alters that term by an amount hardly greater than the experimental error in the term itself, in accord with the theory of specific ionic interaction. Hitchcock (74) has discussed a suggestion of Scatchard that a cell reversible not only to hydrogen ion but also to another univalent cation be utilized for measuring m_H, since the ratio of activity coefficients of two ions of the same charge would be practically unity in solutions of moderate concentration. Redlich and Klinger (129) have studied such a cell: namely,

H_2; solution, TlBr (satd.), AgBr; Ag Cell XI

Inasmuch as the molalities of thallous and bromide ions are equal, the E.M.F. of this cell yields a measurement of $a_H\ (f_{Br}/f_{Tl})^{1/2}$. Unfortunately, the ions appearing in the activity-coefficient ratio are of unlike charge. For this reason, the ratio may depart from unity at relatively low ionic strengths. When the solubility of thallous bromide in the solution is known, $m_H f_H/f_{Tl}$ can also be determined. The numerical values of this quantity should be approximately equal to m_H at low and moderate concentrations, for the hydrogen ion and thallous ion bear the same charge and their concentrations are small with respect to the total salt concentration.

VIII. ESTABLISHMENT OF A UNIFORM SCALE OF paH

The conditions under which one anion can be substituted for another without a sensible change in the activity-coefficient term are obviously of concern in any attempt to select a series of uniform paH standards. Insofar as ratios of certain ionic activity coefficients are involved, one need not rely wholly on theory. It is important first of all that the ionic strengths and the compositions of the buffer solutions with respect to cations be the same. In general, sodium and potassium ions have similar effects, but lithium, barium, strontium, calcium, and zinc ions produce rather large changes in $(f_{HA}f_{Cl}/f_A)$ (116, 117). If undissociated weak acid is present, its concentration should be the same in each buffer solution (118, 137).

TABLE 13

Ratios of activity coefficients of halide ions in phosphate buffer solutions compared with ratios of mean activity coefficients of halides and halogen acids in their pure aqueous solutions

IONIC STRENGTH	$\log \frac{f^0_X}{f^0_{Cl}}$	$2 \log \frac{f_{HX}}{f_{HCl}}$	$2 \log \frac{f_{NaX}}{f_{NaCl}}$	$2 \log \frac{f_{KX}}{f_{KCl}}$
X = Br				
0.05	0.002	0.006		
0.07	0.004	0.008		
0.10	0.005	0.009	0.003	0.002
0.15	0.006	0.012		
0.20	0.008	0.017	0.006	0.006
0.25	0.010	0.019		
X = I				
0.05	0.004	0.014		
0.07	0.007	0.020		
0.10	0.009	0.023	0.012	0.008
0.15	0.012	0.033		
0.20	0.016	0.045	0.022	0.018
0.25	0.019	0.051		

A. *Activity coefficients of ions of the same charge*

The ratio of the activity coefficient of chloride ion to that of bromide or iodide ion in pure phosphate buffers can be obtained from $\log f^0_r$ or from $-\log (f_H f_X m_H)^0$ listed in the tables of the foregoing section:

$$\log (f^0_X/f^0_{Cl}) = \log (f_H f_X m_H)^0 - \log (f_H f_{Cl} m_H)^0 = 2 \log (f^0_{HX}/f^0_{HCl}) \qquad (49)$$

As before, the superscripts in equation 49 designate a pure phosphate buffer without halide. The ratios of the ionic activity coefficients in phosphate buffers are compared in table 13 with the ratios of the mean activity coefficients of the sodium and potassium halides and of the halogen acids in their pure aqueous solutions (64).

oxalate in the molal ratio 1:5 is plotted in figure 8 as a function of ionic strength. The p_2H, p_3H, p_4H, and p_5H curves are again labeled 2, 3, 4, and 5, respectively. The upper dashed line locates the p_1H curve when a_i is 6, and the lower line is computed for $\mathring{a}_i = 4$ (equation 36). The paH was derived from the electromotive force of hydrogen–silver chloride cells without liquid junction (125). The activity coefficient of hydrochloric acid used in the calculation of p_2H by equation 35b was the average of f_{HCl} in aqueous solutions of sodium chloride and of potassium chloride. It is evident that the four scales agree somewhat more closely for oxalate solutions than for phosphates.

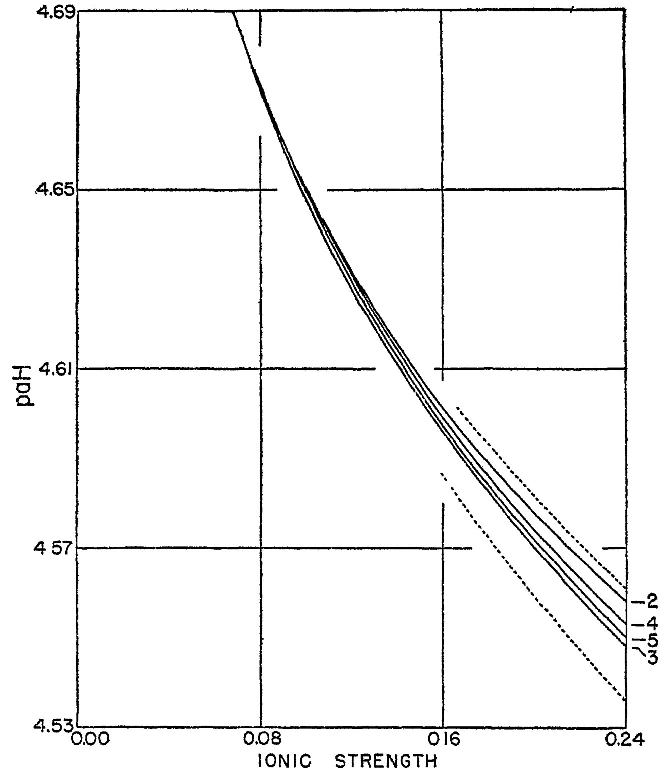

FIG. 8. p_2H, p_3H, p_4H, and p_5H of oxalate buffer solutions as a function of ionic strength. The molal ratio of potassium binoxalate to sodium oxalate is 1:5. The values were derived from the electromotive force of hydrogen-silver chloride cells without liquid junction. Curves representing the four scales are labeled 2, 3, 4, and 5. The dashed lines indicate the course of the curve of p_1H for a_i values of 6 (upper line) and 4 (lower line).

The location of the true $-\log a_H$ in figures 7 and 8 can, of course, never be ascertained. All of these reasonable estimates of $-\log a_H$ agree at ionic strengths below 0.01 to 0.02, however, and there the paH can be said to possess some significance in terms of activity. Thus it may prove desirable to impose an upper limit of 0.02 on the ionic strength of primary standards of paH. Studies of other buffer systems will aid in establishing a limit of general applicability.

satisfactorily compensated in the calculation of p_4H or p_5H. Only p_2H exhibits substantial agreement, and this quantity is considerably higher than the other four. Inasmuch as the activity coefficient of hydrochloric acid is lower in the presence of potassium and sodium salts than in pure aqueous solutions of the acid, these p_2H values are understandably too high. Unfortunately, small systematic changes in log f_r^0, within experimental error, may lead to a different a^0 and different β^0 (equation 48), and p_4H and p_5H may be significantly changed thereby (5).

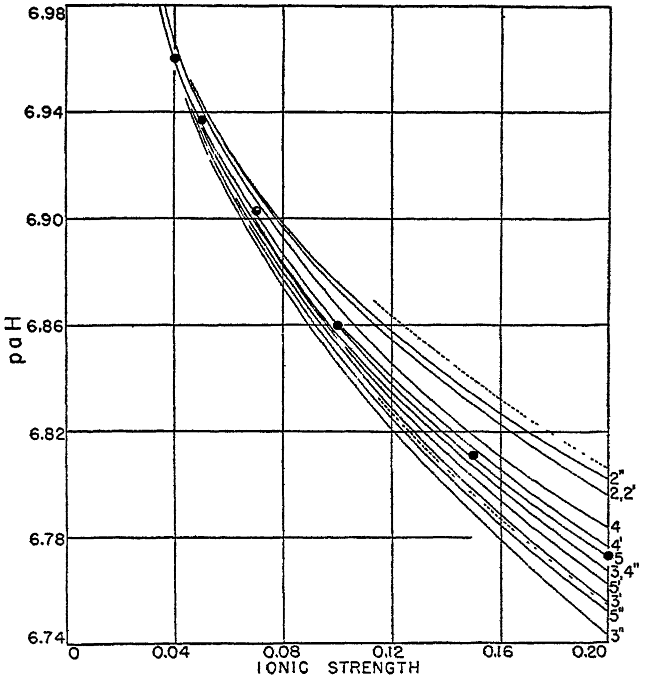

FIG. 7. p_2H, p_3H, p_4H, and p_5H of phosphate buffer solutions as a function of ionic strength. Curves representing the four scales are labeled 2, 3, 4, and 5. The values were derived from the electromotive force of cells with silver–silver chloride electrodes (unprimed), silver–silver bromide electrodes (single prime), and silver–silver iodide electrodes (double prime). The dashed lines indicate the course of the curve of p_1H for a_i values of 8 (upper line) and 3 (lower line).

Figure 7 illustrates the change of p_2H, p_3H, p_4H, and p_5H for equimolal phosphate buffer solutions with changing ionic strength. The lines representing the several scales are labeled 2, 3, 4, and 5. The results derived from bromide cells are marked with a single prime and those from iodide cells with a double prime. Lines unmarked save for the identifying figure represent data from the chloride cells. The upper and lower dashed lines locate the p_1H curve when a_i is arbitrarily assigned the extreme values of 8 and 3 for the computation. The molality of each phosphate salt is one quarter of the ionic strength.

The paH of buffer solutions composed of potassium binoxalate and sodium

It is noteworthy that $-\log (f_H f_X m_H)^0$ decreases as X increases in atomic weight. This change is to be expected if the activity coefficients of the halide ions are in the same order as the mean activity coefficients of the alkali halides and those of the halogen acids. For the same reason, $\log f_r^0$ increases from chloride to iodide. Hence, p_3H values computed by equation 43 from measurements of chloride, bromide, and iodide cells differ more from one another than do the values of $-\log (f_H f_X m_H)^0$. This normal decrease of pwH from chloride to iodide is not

TABLE 11

Parameters of equation 48 for log $(f_{H_2PO_4} f_X / f_{HPO_4})$ *in phosphate buffers without halide*

X	α^0	β^0	Δ
Cl	4.4	0.054	0.0002
Br	4.2	0.069	0.0000
I	4.0	0.079	0.0003

TABLE 12

paH values for phosphate buffer mixtures: KH_2PO_4 (m_1), Na_2HPO_4 (m_1), NaX $(m_2 = 0)$, *from the* E.M.F. *of cells without liquid junction at 25°C.*

m_1	p_1H $(a_i = 4)$	p_2H (EQUATION 35b)	p_3H	p_4H	p_5H
			X = Cl		
0.0125	6.935	6.942	6.936	6.940	6.937
0.0175	6.900	6.910	6.901	6.907	6.903
0.025	6.858	6.873	6.859	6.867	6.862
0.0375	6.806	6.830	6.807	6.819	6.811
0.05	6.768	6.796	6.768	6.784	6.773
0.0625	6.736	6.774	6.736	6.756	6.742
			X = Br		
0.0125	6.933	6.944	6.932	6.937	6.934
0.0175	6.896	6.910	6.895	6.902	6.897
0.025	6.853	6.873	6.852	6.862	6.855
0.0375	6.800	6.829	6.798	6.814	6.803
0.05	6.760	6.796	6.755	6.776	6.762
0.0625	6.726	6.774	6.721	6.747	6.729
			X = I		
0.0125	6.931	6.945	6.929	6.935	6.931
0.0175	6.893	6.913	6.891	6.899	6.893
0.025	6.849	6.876	6.845	6.856	6.849
0.0375	6.794	6.834	6.789	6.807	6.794
0.05	6.752	6.802	6.743	6.767	6.752
0.0625	6.717	6.781	6.708	6.738	6.717

The parameters α^0 and β^0, obtained by the method of least squares, are listed in table 11. The average difference, Δ, between the "observed" values of $\log f_r^0$ and those calculated by equation 48 is given in the last column.

The paH of equimolal mixtures of potassium dihydrogen phosphate and disodium hydrogen phosphate on the several scales based upon measurements of cells without liquid junction can now be compared. Table 12 is a summary of the results computed from cells with silver chloride, silver bromide, and silver iodide electrodes. The differences among paH values on the several scales are negligible at low ionic strengths though appreciable at the higher concentrations. The p_1H value is strongly influenced in concentrated solutions by the value of a_i arbitrarily chosen. The p_2H was computed from $-\log\,(f_H f_X m_H)^0$ by equations of the form of equation 35b together with the mean activity coefficients of hydrochloric acid (58), hydrobromic acid (63), and hydriodic acid (65) in their aqueous solutions at the appropriate ionic strength.

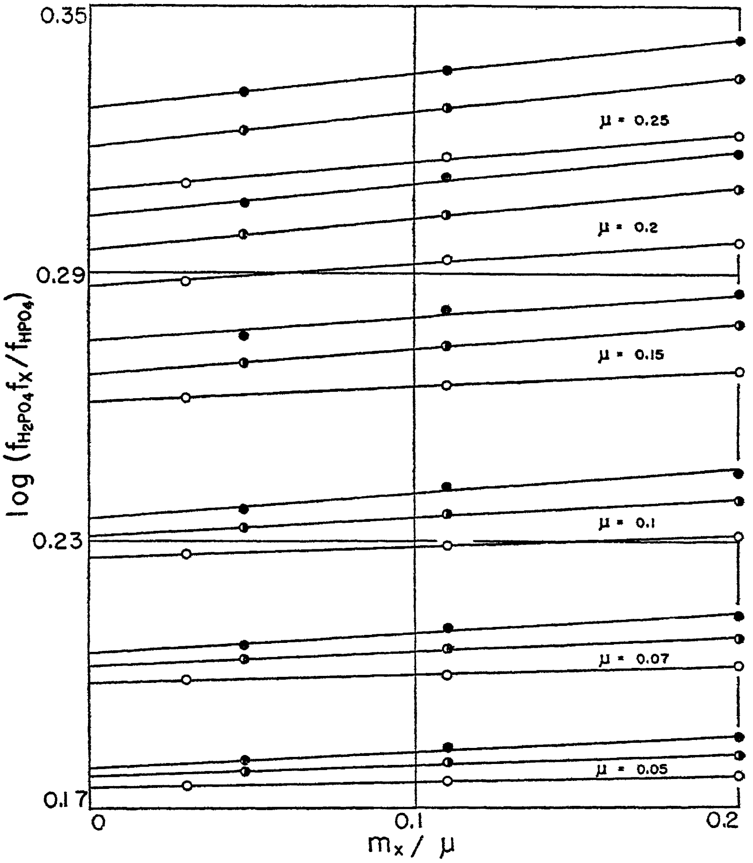

FIG. 6. Log ($f_{H_2PO_4} f_X / f_{HPO_4}$) plotted as a function of the fractional contribution of halide, NaX, to the total ionic strength. For the lower curve of each group, X is chloride; for the middle curve, X is bromide; for the upper curve, X is iodide.

used to compute $\log f_r$ in the buffer solutions containing sodium chloride. The values of the parameters are to be found in an earlier paper (8).

The convergence of the plots of $\log f_r$ at low ionic strengths, though incomplete, is in agreement with a principle of Brønsted (23) referred to earlier in this paper. The activity coefficients of hydrochloric, hydrobromic, and hydriodic acids at zero concentration in a phosphate medium depend as a first approximation only on the specific nature of the phosphate salts.

TABLE 10

Log f_r^0 and $-$ log $(f_H f_X m_H)^0$ for phosphate buffer solutions

IONIC STRENGTH	LOG f_r^0	$-$LOG $(f_H f_X m_H)^0$
	X = Cl	
0.01	0.089	7.109
0.05	0.1748	7.023
0.07	0.1983	7.000
0.10	0.2263	6.972
0.15	0.2610	6.937
0.20	0.2870	6.911
0.25	0.3084	6.890
	X = Br	
0.01	0.090	7.108
0.05	0.1772	7.021
0.07	0.2020	6.996
0.10	0.2310	6.967
0.15	0.2672	6.931
0.20	0.2952	6.903
0.25	0.3183	6.880
	X = I	
0.01	0.091	7.107
0.05	0.1790	7.019
0.07	0.2048	6.993
0.10	0.2350	6.963
0.15	0.2730	6.925
0.20	0.3028	6.895
0.25	0.3267	6.871

The last column of table 10 gives $-\log\,(f_H f_X m_H)^0$, obtained from $\log f_r^0$ by equation 28, for equimolal phosphate buffer solutions in the absence of halide. Hydrolysis of the secondary anion and ionization of the primary anion are so small that the second term on the right of equation 28 can be ignored.

In order to calculate p_4H and p_5H for phosphate buffer solutions by equations 44 and 45, β^0 must be found. For this purpose, the values of $\log f_r^0$ given in table 10 for the chloride, bromide, and iodide series were fitted to equations of the type:

$$\log f_r^0 \equiv \log \left[\frac{f_{H_2PO_4} f_X}{f_{HPO_4}}\right]^0 = \frac{2A\sqrt{\mu}}{1 + Ba^0\sqrt{\mu}} + \beta^0 \mu \qquad (48)$$

and

$$H_2;\ KH_2PO_4\ (m_1),\ Na_2HPO_4(m_1),\ NaI\ (m_2),\ AgI;\ Ag \qquad \text{Cell IX}$$

were made at 25°C.

A comparison of the experimental results for solutions that contained sodium halide at a molality equal to that of each phosphate salt with similar data for phosphate–chloride mixtures (8) is made in figure 5. The quantity plotted as ordinate we have called pwH. When the three curves, plotted from measurements at sufficiently high concentrations so that the buffer ratio is always unity, are extended to zero ionic strength they meet at 7.198, the value of p*K* for the second dissociation of phosphoric acid at 25°C. (6, 8). The separation of these three curves at a given ionic strength decreases as the ratio of halide to phosphate decreases, but the curves fail to meet, if the ionic strength exceeds 0.05, even at zero concentration of halide.

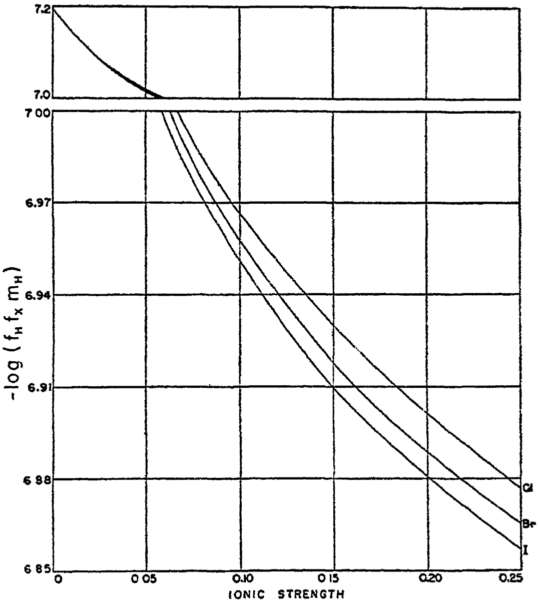

FIG. 5. Observed values of $-\log\ (f_H f_X m_H)$ in equimolal phosphate buffers containing sodium halide (NaX) at a molality equal to that of each phosphate salt plotted as a function of ionic strength.

The activity-coefficient term, $\log f_r$, in phosphate–halide mixtures is defined by

$$\log f_r \equiv \log\ (f_{H_2PO_4} f_X / f_{HPO_4}) \qquad (47)$$

where X represents chloride, bromide, or iodide ion. The limiting values of $\log f_r$ in phosphate buffers without sodium chloride, sodium bromide, or sodium iodide were obtained from plots of $\log f_r$ with respect to m_X/μ, as shown in figure 6. This limiting quantity, termed $\log f_r^0$, is listed in table 10. Equation 37 was

TABLE 9

paH of buffer solutions without chloride at 25°C.

BUFFER	MOLALITY OF EACH COMPONENT	IONIC STRENGTH	p_1H ($a_i = 4$)	p_1H ($a_i = 6$)	p_2H (EQUATION 35a)	p_2H (EQUATION 35b)	p_3H	p_4H	p_5H
Acid potassium phthalate	0.05	0.053	4.002	4.011	4.008	4.007			4.005
Acetic acid, sodium acetate	0.01	0.01	4.717	4.720	4.717	4.718			
	0.1	0.1	4.648	4.663	4.660	4.657			
Acid potassium phthalate, dipotassium phthalate	0.01	0.04	5.169	5.177		5.172	5.170	5.164	5.168
	0.02	0.08	5.098	5.111		5.105	5.100	5.089	5.096
	0.05	0.2	4.991	5.013	5.015	5.009	4.996	4.969	4.987
	0.1	0.4	4.907	4.940		4.942	4.919	4.919	4.902
Potassium dihydrogen phosphate, disodium hydrogen phosphate	0.005	0.02	7.017	7.022		7.017	7.018	7.019	7.018
	0.01	0.04	6.956	6.964		6.959	6.958	6.961	6.959
	0.025	0.1	6.856	6.871	6.866	6.866	6.858	6.865	6.860
	0.05	0.2	6.767	6.789	6.789	6.786	6.767	6.783	6.772
	0.1	0.4	6.663	6.696		6.698	6.660	6.693	6.671
Potassium *p*-phenolsulfonate, sodium potassium *p*-phenolate sulfonate	0.01	0.04	8.841	8.849		8.844	8.857	8.852	8.855
	0.025	0.1	8.770	8.785	8.778	8.779	8.799	8.789	8.796
	0.05	0.2	8.715	8.737	8.735	8.733	8.760	8.740	8.753
	0.1	0.4	8.662	8.695		8.697	8.730	8.691	8.717
Borax	0.01	0.02	9.177	9.182	9.176*	9.177			
	0.025	0.05	9.172	9.181	9.172*	9.176			

* Reference 109.

The separation formula of equation 38 similarly leads to

$$p_4H \equiv -\log (f_H f_{Cl} m_H)^0 - \frac{1}{2}\log f_r^0 + \frac{3}{2}\beta^0\mu$$

$$= pK - \log (m_{HA}/m_A) - \frac{3}{2}\log f_r^0 + \frac{3}{2}\beta^0\mu \qquad (44)$$

when chloride is absent, and equation 40a gives

$$p_5H \equiv -\log (f_H f_{Cl} m_H)^0 - \frac{1}{2}\log f_r^0 + \frac{1}{2}\beta^0\mu$$

$$= pK - \log (m_{HA}/m_A) - \frac{3}{2}\log f_r^0 + \frac{1}{2}\beta^0\mu \qquad (45)$$

The p_4H values of phosphate–chloride mixtures and of phenolsulfonate–chloride mixtures have been reported (6, 12). The paH of mixtures of acid potassium phthalate, phthalic acid, and potassium chloride (49) was computed from the compositions of the mixtures with the aid of a_i and β_i derived in the manner described earlier in this section. Of the published pH values for buffer solutions without chloride, those for mixtures of potassium *p*-phenolsulfonate and sodium hydroxide (7) were computed on the p_4H scale, and those for mixtures of potassium dihydrogen phosphate and disodium hydrogen phosphate (8) and mixtures of acid potassium phthalate and dipotassium phthalate (47) are on the p_5H scale. Inasmuch as the ionic parameters determined from studies of mixtures of primary and secondary phthalates with potassium chloride were used in its determination, the pH of solutions of acid potassium phthalate (50) is also based upon the p_5H scale. These scales are related by the equation:

$$p_4H = p_5H + \beta^0\mu = p_3H + \frac{3}{2}\beta^0\mu \qquad (46)$$

The paH values at 25°C. of some chloride-free buffer solutions on the several scales discussed in this section and the foregoing one are given in table 9. In an attempt to estimate f_{HCl} in these buffer solutions for the computation of p_2H by equation 35b, the average of the activity coefficient of hydrochloric acid at zero concentration in solutions of sodium chloride and in solutions of potassium chloride of the appropriate ionic strength has been employed. This quantity was calculated from data given by Harned (53) and by Harned and Hamer (61).

E. Use of electrodes reversible to bromide and iodide ions

The chloride ion evidently plays a unique and important rôle in these paH equations. Equimolal mixtures of potassium dihydrogen phosphate and disodium hydrogen phosphate have therefore been studied in an effort to determine to what extent the value of paH on these several scales depends upon the reference electrode and the added halide (5). Electromotive-force measurements of cells analogous to type III,

H_2; KH_2PO_4 (m_1), $Na_2HPO_4(m_1)$, NaBr (m_2), AgBr; Ag Cell VIII tions, the last terms of equations 38, 40, and 40a would disappear. From a practical standpoint, this change of assumptions would not have a large effect on the pH values assigned to phosphate buffers, for $\frac{1}{2}\beta^0\mu$ is only 0.003 for a mixture of 0.025 *m* potassium dihydrogen phosphate and 0.025 *m* disodium phosphate, and 0.011 for a mixture in which the concentration of each phosphate salt is 0.1 *m*.

Hamer and Acree (47) have computed β_i for chloride, acid phthalate, and phthalate ions from the observed change of β^* with change of $m_{\mathrm{Ph}}/m_{\mathrm{HPh}}$ between 1.00 and 2.02 and $m_{\mathrm{Cl}}/m_{\mathrm{HPh}}$ from 1.0 to 0.093, where Ph is written for phthalate. A constant value of 3.76 for a^* at 0–60°C. was found for all of these different compositions, and this value was therefore assigned to a_i for each ion. The $\beta^*\mu$ term was expressed in terms of ionic β_i values,

$$\beta^*\mu = \beta_{\mathrm{Ph}}m_{\mathrm{Ph}} - \beta_{\mathrm{HPh}}m_{\mathrm{HPh}} - \beta_{\mathrm{Cl}}m_{\mathrm{Cl}} \qquad (41)$$

by a combination of activity-coefficient equations for each ion written in the form

$$-\log f_i = -A\sqrt{\mu}/(1 + 3.76B\sqrt{\mu}) - \beta_i m_i \qquad (42)$$

In this equation the molality of the ion of species *i* replaces the ionic strength, μ, in the last term of equation 32. The experimental values of β^* and the known molalities of the ions were used to set up a series of equations of the same form as equation 41. Each ratio of the three anions gave a different expression, and the three β_i constants were obtained by the method of least squares.

The concept of constant β_i appears to be at variance with the observed change of β^* when a neutral salt, such as potassium nitrate, is added to a buffer–chloride mixture. It has been found that a^* may remain unchanged, but β^* is usually different (9). Inasmuch as the addition of neutral salt produces no change in the molalities of the buffer ions or chloride, the observed change cannot be accounted for by the formulation of equation 41, where constant β_i is assumed.

Insofar as the treatment of solutions of constant buffer ratio and zero chloride-ion concentration is concerned, this method defines a scale equivalent to that employed to express the paH of the phosphate buffer solutions. The paH values computed by equations 29a and 39 with the limiting parameters for solutions without chloride are identical with the pH given by Hamer and Acree. Since the limiting value of β^*, namely β^0, when chloride is absent is $\beta_{\mathrm{Ph}}m_{\mathrm{Ph}} - \beta_{\mathrm{HPh}}m_{\mathrm{HPh}}$ by equation 41, the equation for dividing the experimental activity-coefficient term for phthalate solutions without chloride is the same as equation 40a.

These assumptions form the bases of three different pH scales. When the ionic activity coefficients are separated by assuming the validity of the valence relationships of the limiting law, that is, $f^4_{\mathrm{HA}^-} = f^4_{\mathrm{Cl}^-} = f_{\mathrm{A}^{--}}$, the paH value of the buffer solution without chloride will be called p_3H. It is defined by

$$\begin{aligned} p_3H &\equiv -\log\,(f_{\mathrm{H}}f_{\mathrm{Cl}}m_{\mathrm{H}})^0 - \frac{1}{2}\log f_r^0 \\ &= pK - \log\,(m_{\mathrm{HA}}/m_{\mathrm{A}}) - \frac{3}{2}\log f_r^0 \qquad (43) \end{aligned}$$

a^* disappears from the formal equation for log f_r, analogous to equation 37. Because a^* and β^*, and also a_i and β_i, possess little physical significance, equations 32 and 37 are useful chiefly as interpolation formulas.

Perhaps the simplest means of splitting f_r to obtain f_{Cl} is to assume the validity of the valence relationships in very dilute solutions, that is, $f_{Cl}^4 = f_{HA^-}^4 = f_{A^{--}}$. Log f_{Cl} is thus set equal to $-\frac{1}{2}\log f_r$. In a study of malonate–chloride buffer solutions, Hamer, Burton, and Acree (48) suggested that for the computation of f_{Cl} the experimental values of a^* and β^* be identified with a_i and β_i of equation 32. It is apparent that the measured activity-coefficient term would then be divided according to the formula,

$$\log f_{Cl} = -\frac{1}{2}\log f_r + \frac{3}{2}\beta^*\mu \tag{38}$$

For the malonate solutions, β^* was zero, and the result is the same in this special case as that based upon the assumption of the valence relationships of the limiting law.

In order to compute the paH of equimolal mixtures of potassium dihydrogen phosphate and disodium hydrogen phosphate, Bates and Acree (8) determined a^* and β^* for five ratios of the molalities of sodium chloride and phosphate. The values of these two parameters were extrapolated to the limit of zero sodium chloride. The assumption was made that the limiting values, a^0 and β^0, could be used in equation 32 to compute $f_{H_2PO_4}/f_{HPO_4}$,

$$\log\left[\frac{f_{H_2PO_4}}{f_{HPO_4}}\right]^0 = \frac{3A\sqrt{\mu}}{1 + Ba^0\sqrt{\mu}} + \beta^0\mu \tag{39}$$

and paH by equation 29a. It was reasoned that the numerical values of the parameters of equation 37 in the absence of sodium chloride would be determined chiefly by the properties of the phosphate buffer. The following formulas are involved in this method of separating $f_{H_2PO_4}/f_{HPO_4}$ from the experimentally defined activity-coefficient term of equation 37:

$$\log\left[\frac{f_{H_2PO_4}}{f_{HPO_4}}\right]^0 = \frac{3}{2}\log f_r^0 - \frac{1}{2}\beta^0\mu \tag{40}$$

and

$$\log f_{Cl}^0 = -A\sqrt{\mu}/(1 + Ba^0\sqrt{\mu}) = -\frac{1}{2}\log f_r^0 + \frac{1}{2}\beta^0\mu \tag{40a}$$

where the superscript zeros indicate the value of the quantity in question in the phosphate buffer without sodium chloride. As equation 40a shows, this treatment implies that the salt-effect term, $\beta_{Cl}\mu$, becomes zero in the absence of chloride.

The appearance in these equations of a term involving β^0 is unfortunate, inasmuch as $-\beta^*$, the slope of the extrapolation plots, can be varied somewhat by choice of a^* within about ± 0.2, the usual error in establishing the latter. If $f_{Cl}^4 = f_{HA^-}^4 = f_{A^{--}}$ were employed as a separation formula at all concentranated p_1H. The results of these calculations are given in table 8. The p_1H of the two acid–chloride mixtures is appreciably higher than paH derived from cells with liquid junction, as a comparison with the results in table 7 shows.

If we assign arbitrarily a value of 4 to a_i for the computation of log f_{Cl} by the last term of equation 36, we have in reality another convention that is possibly easier to employ in the determination of paH from measurements of cell III than those suggested by MacInnes and Guggenheim. As table 8 shows, this assumption is substantially equivalent to the MacInnes convention for these mixtures of strong electrolytes and for solutions of hydrochloric acid.

Inasmuch as cell III is reversible to the ions of hydrochloric acid, it is not unreasonable to identify f_{Cl} with the mean activity coefficient of hydrochloric acid in the cell solution. Unfortunately, this mean activity coefficient cannot be determined unless m_H is known. The activity coefficient of the acid in a mixture of strong electrolytes of the same ionic strength and composition with respect to cations is likewise often unknown. In the method proposed by Hamer and Acree (45) and discussed earlier in this section, f_{Cl} is set equal to f_{HCl} in a solution of hydrochloric acid of the same ionic strength for computing the paH of solutions whose pwH is in the vicinity of 1 to 2. Log f_{Cl} is then assumed to vary linearly with pwH. When f_{Cl} is identified with f_{HCl}, either with or without the linear variation, the paH scale so defined will be called p_2H.

TABLE 8

p_1H for solutions of hydrochloric acid and acid–chloride mixtures at 25°C.

SOLUTION	EQUATION 36 $a_i = 4$	EQUATION 36 $a_i = 6$	MAC INNES CONVENTION	GUGGENHEIM CONVENTION
0.01 m HCl	2.043	2.046	2.042	2.043
0.1 m HCl	1.084	1.099	1.085	1.099
0.01 m HCl 0.09 m NaCl	2.092	2.107	2.092	2.103
0.01 m HCl 0.09 m KCl	2.094	2.109	2.095	2.104

$$p_2H \equiv (\text{pwH} - P)/Q \tag{35a}$$

$$p_2H \equiv -\log (f_H f_{Cl} m_H) + \log f_{HCl} \tag{35b}$$

D. Separation of f_{Cl} from the activity-coefficient term

When the buffer solution is composed of the primary and secondary anions of a dibasic or polybasic acid, the experimental values of log f_r can be represented satisfactorily by an equation of the following form (8, 9, 47):

$$\log f_r \equiv \log \frac{f_{HA^-} f_{Cl^-}}{f_{A^{--}}} = \frac{2A\sqrt{\mu}}{1 + Ba^*\sqrt{\mu}} + \beta^* \mu \tag{37}$$

Both a^* and β^* are readily obtained from the experimental log f_r by a process of curve fitting. When HA is a monobasic acid, however, the term that contains

TABLE 7—*Concluded*

SOLUTION	p_iH AT				paH, FROM CELLS WITH LIQUID JUNCTION, AT		REFERENCE (paH)
	0°C.	25°C.	38°C.	50°C.	25°C.	38°C.	
0.01 *m* potassium dihydrogen phosphate + 0.01 *m* disodium hydrogen phosphate	7.079 7.087	6.956 6.964	6.936 6.943	6.933 6.941	6.963		(76)
0.05 *m* sodium tetraborate (borax) + 0.01 *m* sodium chloride	9.501 9.516	9.186 9.201	9.075 9.091	8.998 9.014	9.180†	9.070†	(76, 77)
0.01 *m* sodium tetraborate (borax) + 0.01 *m* sodium chloride	9.448 9.454	9.170 9.176	9.393 9.399	9.008 9.015	9.178†	9.078†	(76, 77)

* At 12°C.

† paH of the buffer without sodium chloride.

Hitchcock and Taylor (76, 77), derived from measurements of cells with liquid junction, is included, as well as the values of MacInnes, Belcher, and Shedlovsky (102) for acid potassium phthalate and the two acetate buffer solutions. Inasmuch as the choice of a_i is almost completely arbitrary, the uncertainty of the p_iH must be considered at least as great as the difference between the two p_iH scales.

It is of interest to compare p_iH obtained from the electromotive force of cell III with paH computed from mean activity coefficients by the conventions of MacInnes and of Guggenheim. Such a comparison is necessarily limited to strong electrolytes. For this purpose we choose 0.01 *m* and 0.1 *m* hydrochloric acid and mixtures of 0.01 *m* hydrochloric acid with 0.09 *m* sodium and potassium chlorides.

The mean activity coefficient of hydrochloric acid, f_{HCl}, in its pure aqueous solution is 0.905 at 0.01 *m* and 0.796 at 0.1 *m* (58, 145). The value of this activity coefficient in the two mixtures can be computed from published data (38, 53, 61). According to the Guggenheim convention, f_H is numerically equal to f_{HCl}. The mean activity coefficient of potassium chloride is 0.902 and 0.770 at 0.01 and 0.1 *m*, respectively (146). These are also the values of f_{Cl}, by the MacInnes assumption, whenever the chloride-ion concentration is 0.01 or 0.1, as it is in each of the four solutions in question. We then compute f_H by the formula, $f_H = f^2_{HCl}/f_{KCl}$, and paH by equation 5. Inasmuch as the logarithms of the mean activity coefficients of both hydrochloric acid and potassium chloride can be satisfactorily expressed in this range of ionic strengths by the last term of equation 36 with suitable choice of a_i (131, 146), these paH values are desig-

TABLE 7

$\mathrm{p_iH}$ from cells without liquid junction compared with paH from cells with liquid junction

The upper $\mathrm{p_iH}$ value was computed with $a_i = 4$, the lower value with $a_i = 6$

SOLUTION	$\mathrm{p_iH}$ AT				paH, FROM CELLS WITH LIQUID JUNCTION, AT		REFERENCE (paH)
	0°C.	25°C.	38°C.	50°C.	25°C.	38°C.	
0.1 *m* hydrochloric acid	1.080 1.094	1.084 1.099	1.088 1.103	1.094 1.109	1.085	1.082	(76, 77)
0.1 *m* potassium tetroxalate		1.497 1.516	1.504 1.522	1.529 1.548	1.480	1.495	(76, 77)
0.02 *m* potassium tetroxalate	1.925 1.932	1.931 1.937	1.942 1.949	1.957 1.964			
0.01 *m* hydrochloric acid + 0.09 *m* sodium chloride	2.091 2.105	2.092 2.107	2.095 2.110		2.058		(76)
0.01 *m* hydrochloric acid + 0.09 *m* potassium chloride	2.093 2.107	2.094 2.109	2.096 2.111		2.075	2.075	(76, 77)
0.03 *m* potassium bitartrate		3.569 3.575	3.556 3.563	3.564 3.571	3.567		(76)
0.1 *m* potassium dihydrogen citrate	3.811 3.826	3.709 3.725	3.687 3.703	3.696 3.713	3.719		(76)
0.02 *m* potassium dihydrogen citrate	3.925 3.929	3.835 3.840	3.818 3.823	3.815 3.821			
0.05 *m* acid potassium phthalate	4.002 4.011	4.002 4.011	4.027 4.036	4.064 4.074	4.010 4.000 4.000*	4.025 4.015	(76, 77) (102) (102)
0.1 *m* acetic acid + 0.1 *m* sodium acetate	4.680 4.694	4.648 4.663	4.653 4.668	4.672 4.687	4.648 4.640 4.650*	4.655 4.635	(76, 77) (102) (102)
0.01 *m* acetic acid + 0.01 *m* sodium acetate	4.746 4.748	4.717 4.720	4.725 4.728	4.745 4.748	4.714 4.700 4.710*	 4.710	(76) (102) (102)
0.025 *m* potassium dihydrogen phosphate + 0.025 *m* disodium hydrogen phosphate	6.979 6.993	6.856 6.871	6.835 6.850	6.833 6.848	6.858	6.835	(76)

corresponded to the appropriate pwH was then interpolated graphically or calculated by means of the equation for the line. The pH of the buffer solution could then, of course, be computed by equation 29. The constants P and Q of the equation

$$\mathrm{pH} = (\mathrm{pwH} - P)/Q \tag{35}$$

at several ionic strengths are given in their paper. The pH of 0.05 m acid potassium phthalate found in this way agreed well with the paH later assigned to this solution (50) on the basis of extensive studies of the equilibria in the phthalate buffer systems (47, 49).

The activity coefficients of chloride ion in pure solutions of hydrochloric acid and potassium hydroxide found by this means for ionic strengths below 0.1 correspond to those calculated by the first term on the right of equation 32 with 5.6 and 3.4, respectively, for a_i. Intermediate values of a_i would be needed for computing f_{Cl} in buffer solutions of intermediate pH. In terms of equation 32, therefore, this method postulates a dependence of a_i and of log f_{Cl} (or log f_{H}) upon the acidity of the solution. Insofar as a decrease of acidity always means a change of composition of the solution away from that of a strong acid and toward that of a strong base, this view is not unreasonable. Hamer and Acree suggest further that the data for the activity coefficient of sodium or lithium hydroxide, instead of potassium hydroxide, be used when sodium and lithium are predominant among the buffer cations. In spite of this refinement, however, the specific effects of ions other than hydrogen, hydroxyl, and the alkalis on the value of f_{Cl} and f_{H} cannot be ignored.

If $-\log f_{\mathrm{Cl}}$ is computed by the first term on the right of equation 32, with arbitrary choice of the value of a_i, a unit of acidity that will be termed $\mathrm{p_iH}$ can be defined with the aid of equation 29:

$$\mathrm{p_iH} \equiv -\log\,(f_{\mathrm{H}}f_{\mathrm{Cl}}m_{\mathrm{H}}) - A\sqrt{\mu}/(1 + Ba_i\sqrt{\mu}) \tag{36}$$

In agreement with Bjerrum's calculation (17), a_i for most strong uni-univalent electrolytes in aqueous solution is in excess of 3.5, and values over 6 are uncommon with electrolytes of this valence type.[12] For this reason, Bates, Siegel, and Acree (11) chose a value of 4.0 for constructing titration curves of monobasic acids in dilute solutions from measurements of cells of type III without liquid junction.

Obviously the differences of $\mathrm{p_iH}$ caused by the choice of different values of a_i disappear in dilute solutions. Consequently, f_{Cl} can be estimated with greater certainty for a dilute buffer than for a solution of higher ionic strength. In table 7 $\mathrm{p_iH}$, computed from the data of table 6 by equation 36, is listed for fifteen solutions. Two values, 4 and 6, were used for a_i. The paH on the scale of where A and B are constants at a particular temperature (105, 138) in the water medium and a_i and β_i are parameters characteristic of the mixture of ions. With this value for f_{Cl}, $\mathbf{a}_H$ could be obtained. In the absence of any information concerning the values of a_i and β_i, relatively large uncertainties must be ascribed to the pH. For accurate work and for standardization purposes, it is necessary to know these values (44).

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[12] The value of a^* (the symbol used in place of a_i when a combination of activity coefficients is being expressed by equation 32) for log $(f_{\mathrm{HPs}}f_{\mathrm{Cl}}/f_{\mathrm{Ps}})$, where Ps is the bivalent p-phenolate sulfonate anion, was found to be 8.0 (12). In calculations of log $(f_{\mathrm{HCO_3}}f_{\mathrm{Cl}}/f_{\mathrm{CO_3}})$, the writer found a value of 10.0 to be consistent with the E.M.F. data of Harned and Scholes (66). Values of 3.5 to 6.0 have been obtained for most other buffer solutions.

Manov, DeLollis, and Acree (107) computed the pH of mixtures of borax and sodium chloride after evaluating f_{Cl} by equation 32 without the term $\beta_i\mu$, which is of secondary importance at low ionic strengths. It was assumed that the activity coefficient of chloride ion in all mixtures of borax and sodium chloride is equal to the mean activity coefficient of sodium chloride in a pure solution of the salt at the same ionic strength. A value of 4.4 was assigned to a_i, inasmuch as the first term on the right of equation 32 represents $\log f_{NaCl}$ at ionic strengths below 0.05 when this value of a_i is used (24, 141). In a later paper (109), results of measurements with varying ratios of sodium chloride to borax were reported. Equation 32, with the same a_i value (4.4) as before, was used for computing the activity coefficient of chloride ion, but $\beta_i\mu$ was replaced by $-Cm_{Cl}$, where C is the slope of the plot of pK',

$$pK' = (E - E^0)/k + \log (m_{HBO_2}/m_{BO_2}) \tag{33}$$

for a given borate buffer solution with respect to the molality of sodium chloride.

The activity coefficient of chloride ion was in effect set equal to the mean activity coefficient of sodium chloride only when chloride was absent. It is apparent from a consideration of equations 16, 28, 32, and 33 that f_{Cl} at ionic strengths below 0.05 was expressed by

$$f_{Cl} = f_{NaCl} f_r / f_r^0 \tag{34}$$

where f_r is $f_{HBO_2} f_{Cl} / f_{BO_2}$ in a mixture of borax and sodium chloride and f_r^0 is the same quantity in a borax solution of the same concentration but without chloride.

The dissociation of HBO_2 may not be the only equilibrium of significance in borax buffers of moderate concentration (89). For this reason, the buffer ratio may depart from unity, and incorrect results are then obtained by equation 29a. Under these circumstances, however, the paH computed from equation 29 will approximate the true value, inasmuch as secondary equilibria influence this computation only through a change in ionic strength. When the concentration of borax is 0.01 M or less, the two equations yield substantially the same result.

In order to determine the pH of 0.05 m acid potassium phthalate, Hamer and Acree (45) constructed plots of $-\log f_{Cl}^0$, that is, $\log (f_H m_H)^0 - \log (f_H f_{Cl} m_H)^0$, where the superscript zero indicates the value of the quantity extrapolated to zero sodium (or potassium) chloride, as a function of $-\log (f_H f_{Cl} m_H)$, which we have called pwH. Equation 13 was assumed to hold for aqueous solutions of hydrochloric acid and potassium hydroxide up to a molality of 0.2. It was then possible to assign values to $\log (f_H m_H)^0$, and hence to $-\log f_{Cl}^0$, in solutions of these strong electrolytes. Straight lines were drawn between $-\log f_{Cl}^0$ in the acid and alkaline solutions at each of several ionic strengths. The value that

Brønsted. The first of these is the principle of specific ionic interaction (21).[11] This theory, which has been able to interpret successfully the properties of many mixtures of strong electrolytes, may be summarized by its two postulates: (*a*) Ions of like charge repel each other so strongly that the interactions of their short-range forces are identical and negligible, and (*b*) each ion exerts a "salting-out effect" on every other ion in the solution, that is, an effect which tends to increase the activity coefficient.

The first of these postulates leads one to expect only small changes in the last term on the right of equation 28 when an anion, A, is substituted for another of like charge. This term would be altered, however, by a change in the kinds of cations. The theory also predicts a linear change of this activity-coefficient term with change of composition, as long as the ionic strength is constant and the kinds of ions remain unchanged. When the change in composition involves a change of ratio of different cations, however, the activity coefficient may not vary in such a simple manner. Beyond these considerations, Brønsted's principle offers no assistance in splitting the activity-coefficient term.

Güntelberg and Schiödt (39) and others (20, 82) have pointed out the usefulness in electrometric work of a kinetic principle set forth by Brønsted (23). According to this principle, the activity coefficients of substances present in small amount in a mixture of electrolytes are virtually independent of the quantities of these substances and are determined solely by the salt present in large amount.

The assumptions that have been used to evaluate the individual activity coefficients will be discussed in the sections to follow. It will be convenient to distinguish among paH values related to these various assumptions. The symbols p_1H, p_2H, etc., will be used to differentiate the several paH scales that will be considered.

C. Estimation of the activity coefficient of chloride ion

It is evidently not impossible to employ cells of type III for the measurement of $-\log m_H$ or $-\log a_H$ of unknown solutions. In addition to the experimental difficulties attending the use of cells of this kind with solutions of unknown composition, it is necessary to evaluate $f_H f_{Cl}$ or f_{Cl} to compute respectively $-\log m_H$ or $-\log a_H$ from equation 29. In order that m_H could be calculated, Hamer (42) suggested that $f_H f_{Cl}$ be computed with the aid of Guggenheim's equation (35) for a "standard" electrolyte, the first term on the right of equation 26,

$$\log f_i = -A\sqrt{\mu}/(1 + \sqrt{\mu}) \qquad (31)$$

where i represents a single ionic species, or that it be set equal to the square of the mean activity coefficient of sodium chloride at the appropriate ionic strength. Hamer and Acree (44) preferred to use the Hückel equation (78) for computing f_{Cl},

$$\log f_i = \frac{-Az_i^2\sqrt{\mu}}{1 + Ba_i\sqrt{\mu}} + \beta_i\mu \qquad (32)$$

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[11] See also Güntelberg (38), Scatchard and Prentiss (141), and chapter 14 of the monograph of Harned and Owen (64).

Such similarities result from similarities in ionic charge–ionic size effects (189) and are very pronounced. Perhaps the greatest differences between these trivalent elements on the one hand and tetravalent thorium on the other are in basicity. The markedly reduced basicity of thorium is, however, but little different from that of cerium(IV). General trends in properties rather than sharp differences are the rule among these materials, and separational procedures involving them are commonly very involved and often only fractional in character.

Quantitative methods for the estimation of thorium are complicated by the same factors. Thorium may be determined readily and with extreme accuracy when present alone, but when other elements, particularly scandium, yttrium, and the rare earth elements, are present, its estimation is difficult and tedious. Even though a number of quantitative procedures have been proposed, really simple and at the same time accurate methods have yet to be developed.

II. Qualitative Detection of Thorium

A. SPECTROSCOPIC DETECTION

Thorium salt solutions show no absorption in the spectral range 2000–10,000 Å. and cannot be identified by direct absorption spectra measurements (92). However, Formánek (85) has shown that addition of the dye alkanet gives violet solutions which show maximum absorption in the range 6055–6081 Å. with thorium chloride and in the range 6066–6084 Å. with thorium nitrate, with bands of lesser intensities in the ranges 5599–5625 Å. and 5195–5222 Å. Unfortunately, salts of lanthanum, cerium, praseodymium, neodymium, erbium, yttrium, and zirconium give solutions with nearly identical absorption spectra, and detection of thorium in their presence would be exceedingly difficult.

The arc and spark spectra of thorium are rich in lines (104, 236). The most intense of these lines have been listed as 4019.137 Å., 3601.040 Å., 3538.75 Å., and 3290.59 Å. (104). These lines may be used for the identification of the element. The characteristic x-ray spectrum is also useful (88, 89).

B. RADIOMETRIC DETECTION

Thorium is a weak alpha emitter of half-life 1.34×10^{10} years. The short range of the emitted alpha particles (2.59 cm. in air at 760 mm. of mercury and 15°C.) and the slowness of the decay process combine to render detection of the element by means of its primary radiation a difficult task. Fortunately, a a number of its decay products, notably mesothorium II, have higher specific activities and may be detected more readily. If radioactive equilibrium has been attained, detection of thorium in this fashion is feasible. However, since uranium materials are often encountered in combination with those of thorium, this method is not necessarily accurate.

C. DETECTION THROUGH REACTIONS OF THE THORIUM ION

Thorium compounds are ordinarily white in the solid state and yield colorless solutions. The nitrate, perchlorate, acetate, sulfate, chloride, bromide, and iodide are the common water-soluble salts. From solutions of such materials, thorium may be precipitated as a white, gelatinous hydrous oxide (214) by aqueous ammonia, soluble metal hydroxides, or ammonium sulfide. The hydrous oxide is not amphoteric, but its precipitation may be inhibited by such complex-forming anions as acetate, tartrate, and citrate. The hydrous oxide may also be precipitated by hydrolytic reactions from hot solutions containing alkali metal thiosulfates, azides, or nitrites.

Soluble carbonates precipitate white basic thorium carbonate, soluble in excess ammonium carbonate solution. Thorium is completely precipitated as carbonate by barium carbonate. Oxalic acid precipitates crystalline normal thorium oxalate from dilute mineral acid solutions. Ammonium oxalate also precipitates thorium, but the precipitate dissolves in an excess of the reagent. In these behaviors thorium ion resembles the ions of the yttrium earths very closely.

Thorium ion is also precipitated as fluoride by either hydrofluoric acid or soluble metal fluorides, as double sulfates by alkali metal sulfates, as hydrated peroxide by hydrogen peroxide, as iodate by soluble iodates even in nitric acid solution, as ferrocyanide by soluble ferrocyanides, and as acid orthophosphate, pyrophosphate, or hypophosphate by the corresponding alkali metal salts. The majority of the thorium salts of organic acids are also water insoluble.

In systematic qualitative analysis, thorium ion is ordinarily concentrated and separated with scandium, yttrium, and the rare earth ions. After removal of scandium, thorium may be detected in the presence of the other materials by selective precipitation (26) from strongly acidic solutions with potassium iodate (186), alkali metal hypophosphates (151, 152, 209, 252), or alkali metal pyrophosphates (52) or from weakly acidic solutions with hydrogen peroxide (16, 28, 258, 259, 260, 262), alkali metal azides (70, 71, 72, 73), sebacic acid (222), *m*-nitrobenzoic acid (193, 194, 195), or sodium thiosulfate after boiling (16, 77, 87, 121, 122). Perhaps the most useful of these qualitative procedures is that employing iodate (120, 186), although zirconium and cerium(IV) materials also precipitate.

In the usual qualitative procedure, thorium ion is separated with the members of the ammonium sulfide group and is concentrated with iron and the other members of the so-called iron subgroup. A number of procedures have been recommended for its further separation. Thus, Browning (45) suggests precipitation of the fluorides of thorium and the rare earth elements from hydrochloric acid solution, followed by decomposition of these materials with concentrated sulfuric acid and precipitation of thorium with thiosulfate. Confirmation by dissolution of the oxalate in ammonium oxalate and reprecipitation with acid is further recommended (45). Noyes and Bray (198, 199, 200) also recommended separation by fluoride precipitation. This is followed by extraction of scandium as a soluble fluo complex ion with ammonium fluoride, decomposition of residual fluorides with perchloric acid, and detection of thorium by a method such as those outlined above. Still another procedure (38) involves precipitation with oxalic acid from a dilute hydrochloric acid solution, followed by extraction with ammonium oxalate solution. Dilution of the extract precipitates any zirconium and yttrium earth elements, and thorium oxalate is then precipitated by adding hydrochloric acid. Confirmation by either the iodate or the pyrophosphate procedure is recommended (38). All these general methods appear to be about equally effective. Microchemically, thorium may be identified as either the oxalate or the sulfate (90).

Thorium gives no characteristic dry reactions (213), and bead tests are equally ineffective. Vortmann (243) has outlined a general qualitative scheme involving dry reactions, although no ultimate provision for the detection of thorium is made. Successive fusions with sodium carbonate and sulfur and with potassium peroxydisulfate convert thorium, zirconium, and the rare earth elements to water-insoluble double sulfates. Separation from all materials except silica, barium sulfate, lead and bismuth compounds, and platinum is said to be effected in this fashion (243).

A number of colorimetric methods for the detection of thorium have been outlined (174, 241, 247, 263), but these procedures are not specific. Thus, the alkanet procedure of Formánek (85) referred to above is useful, but only in the absence of interfering elements. Kaserer (135) reported that as little as 0.1 mg. of thorium nitrate in 100 ml. of solution yielded a recognizable yellow color with pyrogallol aldehyde (2,3,4-trihydroxybenzaldehyde) and a flocculent yellow precipitate upon boiling. Zirconium compounds gave the same behavior, but cerium(III) compounds differed in failing to precipitate upon boiling. Aurintricarboxylic acid (aluminon) was found by Middleton (187a) to yield a bright red lake with thorium materials, but this reaction is sensitive to only one part in 10,000 (241) and is complicated by the similar behavior of rare earth metal and many more common ions (187a). Pavelka (202) obtained a violet coloration with as little as one part of thorium in 125,000 by impregnating paper with alizarin, treating with a slightly acidic thorium salt solution, and exposing to ammonia fumes. Both titanium and zirconium compounds gave reddish colors under similar conditions, but rare earth materials were apparently not investigated. Sodium alizarinsulfonate has been reported by Germuth and Mitchell (94a) to yield a red color with thorium ion, but the reaction is sensitive to only one part of thorium in 200 (241) and is far from specific (94a). Quinalizarin in the presence of sodium hydroxide has been found to give a blue color or precipitate with as little as one part of thorium in 150,000 (148). Both zirconium and the rare earth elements gave similar results, the latter when present to the extent of only one part in 1,000,000. Detection of thorium by means of the orange red color produced by addition of 1 per cent gallic acid solution to an ammoniacal salt solution has also been reported (217), although interference from a number of the rare earth elements occurs. Using tincture of cochineal in a nearly neutral solution, Beck (15) reported the detection of thorium through the production of a blue color. Under comparable conditions, the rare earth elements gave reddish colorations. Kuznetsov (160) obtained brownish yellow, crimson-pink, pink, and blue-violet colorations when thorium salt solutions were treated with 2-(*o*-arsonophenylazo)-*p*-cresol, 1-(*o*-arsonophenylazo)-2-naphthol-3,6-disulfonic acid, 1-(*o*-arsonophenylazo)-2-naphthol-6,8-disulfonic acid, and 3-(*o*-arsonophenylazo)-4,5-dihydroxy-2,7-naphthalenedisulfonic acid, respectively. Such tests could not be applied in the presence of rare earth metal or zirconium ions since these materials, under comparable conditions, yielded colors differing only in shade. The conversion of the yellow 8-hydroxyquinoline derivative of thorium into a red material by excess 8-hydroxyquinoline at temperatures above 70°C. (115) may perhaps be of use in the detection of thorium in the presence of the rare earth elements, since the corresponding compounds of the latter materials are uniformly yellow regardless of conditions (92). Useful summaries of the applicabilities and limitations of these colorimetric tests are given by van Nieuwenburg *et al.* (241) and by Wenger and Duckert (247).

III. Separation of Thorium from Other Elements

The most abundant natural sources of thorium are monazite and the monazite sands, its occurrence as orthosilicate (thorite) and oxide (thorianite) being of but little importance. The common natural associates of thorium are, therefore, scandium, yttrium, the rare earth elements, titanium, zirconium (plus hafnium), uranium, iron, aluminum, calcium, silica, and phosphorus as phosphate. Removal of the common elements from thorium presents no great problem, and separation from the periodic group IV analogs is not particularly difficult. However, the similarities existing between thorium compounds and those of scandium, yttrium, and the rare earth elements as mentioned in a previous section render the removal of these elements from thorium extremely difficult. The general methods of treating thorium minerals have been summarized in a number of publications (26, 38, 54, 120, 124, 176, 183, 215, 224) and need not be discussed here.

A. SEPARATION FROM THE COMMON ELEMENTS

General separations from the common elements have been indicated in the section on qualitative detection. These procedures are usually sufficiently quantitative in character to permit their application without essential modification. Perhaps the best general separational method involves precipitation of thorium with oxalic acid from slightly acidic solutions (37, 109, 224). Oxalate precipitation is effective not only in separating thorium from all the common metals but in removing phosphate as well. Of the various other procedures suggested for the removal of phosphate (224), precipitation of thorium as iodate from nitric acid solutions (180, 186) or as hydrous oxide with sodium hydroxide after digestion with sodium carbonate (124) or fusion with caustic alkali (46) appear to be the most effective. Baskerville's procedure (12, 13) of volatilizing phosphorus by high-temperature reduction of monazite with coke in the presence of lime and fluospar appears to offer no advantages because of the specialized equipment involved. The same may be said of the rather similar processes of Troost (235) and Weiss (245). Silica is usually removed as such after dehydration in the presence of acids. Iron, which is often a persistent impurity, may be removed through oxalate precipitation, by extraction as ferric chloride with ether (170), by precipitation as sulfide from tartrate medium (229, 230), or by electrolysis (134, 219). An electrolytic procedure depending upon amalgam formation has been suggested for the removal of barium ion (173).

B. SEPARATION FROM LESS COMMON ELEMENTS OTHER THAN YTTRIUM AND THE RARE EARTH ELEMENTS

Precipitation with oxalic acid from acidic solution frees thorium from essentially all of the less familiar elements except scandium, yttrium, and the rare earth metals. This procedure is particularly effective in removing titanium, zirconium, hafnium, and uranium compounds (38, 111, 120, 215). In a modified version, ammonium oxalate may be added in excess and thorium precipitated as oxalate by addition of acid. Removal of zirconium by this means is very effective (38, 127, 128). Precipitation with iodate does not free thorium from zirconium compounds, but treatment of the iodate precipitate with oxalic acid dissolves out zirconium materials effectively (38, 180, 183). Fusion with potassium acid fluoride to produce water-soluble fluo complexes, K_2MF_6, of titanium and zirconium and water-insoluble thorium fluoride has also proved useful for separation from these materials (69). Patents covering the removal of thorium and rare earth materials from titanium, zirconium, and iron compounds by precipitation of the former as fluorides have been issued (164). A partial separation of thorium from zirconium is effected by evaporation of sulfate solutions containing thallous sulfate (83), a double thorium salt, $2Th(SO_4)_2 \cdot 7Tl_2SO_4$, crystallizing first and being followed by a mixture containing $Zr(SO_4)_2 \cdot 2Tl_2SO_4 \cdot 4H_2O$. This separation is not efficient. Ammonium salicylate is reported to precipitate thorium but not titanium from a mixed salt solution (76). The bulk of the titanium and zirconium materials present in monazite remain as insoluble residues after the mineral is digested with sulfuric acid and then treated with cold water (124, 224). Many procedures, such as precipitation with pyrophosphate (49, 52), with hypophosphate (107, 252), with amines (105, 207), with bases such as lead carbonate (95), and with *m*-nitrobenzoic acid (193, 194, 195), are not effective in removing zirconium and its homologs. Removal of tungsten by extraction as water-soluble tungstate after fusion with sodium carbonate has been reported (257).

Similarities in basicities and complex-forming tendencies complicate the removal of scandium compounds from those of thorium. An excellent critical review of available methods has been given by Fischer and Bock (84). Precipitation with ammonia, with oxalic acid, with hydrofluoric or fluosilicic acid, with sodium alizarinsulfonate, or with phenylarsonic acid is not effective (84). Of the effective procedures (84), those involving excess ammonium fluoride (181) or excess potassium iodate in nitric acid solution (180) preferentially precipitate thorium, while those involving ammonia in ammonium tartrate solution (182) or boiling sodium carbonate solution (129, 187, 225) preferentially precipitate scandium. The ammonium fluoride and sodium carbonate procedures are the most commonly used. Separation by extraction of scandium thiocyanate with ether from aqueous solution (84), by fractional sublimation of the chlorides

(84), and by selective sublimation of scandium as acetylacetonate (84) have also been recommended for the complete removal of scandium from thorium.

C. SEPARATION FROM YTTRIUM AND THE RARE EARTH ELEMENTS

Separation of thorium from yttrium and the rare earth elements, while not as difficult as separations among the latter elements, is, nevertheless, far from simple. The abundant literature which has accumulated on methods for such separations (24, 25, 26, 52, 120, 124, 163, 167, 175, 178, 183, 224) may be cited as evidence for the complexity of the problem. In spite of the numerous investigations which have been carried out and of the variety of procedures which have been suggested, methods which combine rapidity with high efficiency have yet to be developed.

Proposed and recommended procedures may be classified conveniently as:

1. Those dependent upon differences in ease of accepting coördinating groups.
2. Those dependent upon differences in basicity.
3. Those dependent upon differences in solubilities of particular compound types.
4. Those dependent upon other differences in properties.

In all instances, separation from cerium(IV) compounds must be given special consideration, for in this state of oxidation cerium differs but little from thorium in the characteristics of its compounds.

1. Methods dependent upon differences in coördinating tendencies

Considerations based upon ionic charge–ionic size relationships (189) suggest sizable differences between thorium and these trivalent elements in ease of coördinate-bond formation. Thus, thorium would be expected to form coördination compounds much more readily than the cerium earth elements and, but to a lesser extent, more readily than yttrium and the yttrium earth elements. Only slight differences, however, would be expected between thorium and cerium(IV). Experimental observations are in accord with these predictions, and several useful methods of separation which take advantage of observed differences have been proposed.

(a) The oxalate procedure

Based upon an early observation by Bahr (9) that the oxalate of "wasium" (i.e., thorium) dissolved in ammonium oxalate solution, the method was first used for the purification of thorium compounds by Bunsen (47, 48), who found treatment of mixed rare earth and thorium oxalates with hot ammonium oxalate solution to dissolve the thorium material completely and the rare earth materials to only a slight extent. Dilution with water precipitated dissolved rare earth oxalates but was without effect upon the thorium compound. While several repetitions of the procedure were required, Bunsen found it to work to advantage upon thorium compounds which had been precipitated previously with sodium thiosulfate (48).

The basis for the method is apparent in the relative solubility data for thorium and rare earth oxalates in excess ammonium oxalate solution as given by Brauner (36, 37). Expressed in terms of the relative quantities of oxides dissolved, these solubilities were determined to be: Th, 2663; Yb, 105; Y, 11.0; Ce(III), 1.8; Nd, 1.5; Pr, 1.2; and La, 1.0. It is obvious that while thorium oxalate is by far the most soluble, appreciable quantities of rare earth oxalates, particularly those of the yttrium earths, may be expected to dissolve. The solubility of thorium oxalate as a function of ammonium oxalate concentration has been determined by Hauser and Wirth (106). Expressed as grams of ThO_2 per 100 ml. of solution at various normalities of ammonium oxalate, their values are: 0.01 *N*, 0.004 g.; 0.1 *N*, 0.22 g.; 0.5 *N*, 1.76 g.; saturated, 14.83 g. Thus, extraction can be effective only at high oxalate concentrations.

The composition of the complex oxalate derivative existing in solution has not been determined with accuracy. Brauner (36, 37) reported that 3.59 moles of oxalate ion were required to keep each mole of thorium in solution and suggested the formula $(NH_4)_2C_2O_4 \cdot 2Th(C_2O_4)_2 \cdot 7H_2O$ for the product crystallized from such solutions. Both this compound and a dihydrate were obtained by James, Whittemore, and Holden (130), and Hauser and Wirth (106) postulated the existence of the complex $[Th_2(C_2O_4)_5]^{--}$.

That the oxalate procedure effected only an incomplete separation of thorium from the rare earth elements and yttrium was recognized early (131), although Hintz and Weber (121, 122) found the method to be superior to that involving thiosulfate on a comparative basis. However, Drossbach (77) found thorium material extracted in this fashion to be contaminated with comparatively large amounts of the yttrium earths, and Benz (16), as a result of an extremely critical survey, reported the loss of as much as half the original thorium as well as an appreciable contamination of the product by cerium. Although the method has been a popular one (27, 32, 33, 69, 93, 97, 98, 99, 127, 128, 166, 178, 190, 214, 250, 256), the consensus of opinion at present is that it is inefficient (26, 120, 167, 224), particularly when relatively small quantities of thorium are to be removed from comparatively large amounts of rare earth materials (183).

From its solution in ammonium oxalate, thorium may be recovered by precipitation with acids (36, 37, 121), by precipitation with ammonia (99, 121), or by evaporation and ignition to oxide (47, 48). Zirconium oxalate is extracted with thorium oxalate but does not precipitate on acidification (55, 127, 128), while the major portion of dissolved yttrium earth oxalates is precipitated by dilution (47, 48, 224). Important modifications of the procedure involve dissolution of precipitated thorium oxalate in either ammonium acetate (97, 98, 99), ammonium carbonate (131), or sodium carbonate (147) solution. No advantages over the original oxalate procedure are apparent in such modifications. All these procedures entail repeated precipitations and extractions, and in every case prior reduction of cerium is desirable to prevent excessive contamination by that element.

(b) The carbonate procedure

Based upon an early observation by Damour (65) that thorium carbonate is more soluble in solutions containing excess carbonate than are the rare earth carbonates, this method is essentially the same as the oxalate procedure just discussed. In fact the dissolution of thorium oxalate in ammonium (131) or sodium (147) carbonate solution may be regarded as a variation of the general method. Separation by means of ammonium carbonate is incomplete (224), and no more than a concentration of the thorium is achieved. On the other hand, several procedures involving separation of thorium by dissolution in sodium carbonate or bicarbonate solution have been patented (61, 164, 165, 211). The procedure was recommended by Witt (255) for the elimination of cerium from thorium, but it has found little favor in recent years and appears to be about as inefficient as the oxalate procedures (224). Repeated extraction and reprecipitation is necessary, and the solubilities of the carbonates of the yttrium group of elements are sufficient to cause interferences. Thorium may be recovered from solutions containing the carbonate complex by evaporation or by precipitation with sodium hydroxide (165). The composition of the carbonate complex is not known.

(c) Miscellaneous procedures

Treatment of saturated sodium sulfite solution with a neutral solution of thorium and rare earth salts has been found (14, 56, 57) to precipitate the cerium earths completely but to leave most of the thorium in solution. However, Grossman (103) reported the separation to be inefficient in the presence of sizable quantities of the cerium earths, and but little attention has been paid to the method.

Few, if any, other procedures involving the formation of complex thorium compounds in solution have been proposed. The field of inner complexes has also been explored only rather superficially. The precipitation of thorium by a good many organic acids doubtless involves the pronounced tendency of thorium ion to act as an electron-pair acceptor, and in many instances chelate structures probably result. However, insufficient information is available to permit treatment of these cases as such, and they are, as a result, lumped together in the section on solubility differences. Formation of a chloroform-soluble acetylacetone derivative of thorium, $Th(CH_3COCH{=}COCH_3)_4$ (237, 238), by direct precipitation from aqueous solution may be cited as a possible means of separation, since the rare earth elements do not behave similarly. Correspondingly, the greater ease of formation and greater solubility in solvents such as chloroform and trichloroethylene of the 8-hydroxyquinoline derivative of thorium (92) may possibly be used to advantage in effecting separations. Much profitable investigative work remains to be done in this field.

2. Methods dependent upon differences in basicity

Comparisons of properties which measure the attraction of metal ions for electrons or anions indicate the basicity of the thorium ion to be much less than that of scandium, yttrium, or any trivalent rare earth ion (189). Such sizable differences render basicity methods far more feasible for the separation of thorium from these elements than for separations within the rare earth group (189). Numerous methods depending upon basicity differences have been proposed and used. Although some differences exist between thorium and cerium(IV) materials, these differences are so small as to render separation of these two elements impractical without prior reduction of cerium(IV) to cerium(III).

(a) Separation by alkaline precipitants

While the hydrous oxides and hydroxides of yttrium and the rare earth elements precipitate (at 25°C.) over the general pH range of 6.2 to 8.4 (41, 43, 189), hydrous thorium oxide forms at a much lower pH. Thus, by electrometric titration of thorium chloride solution at room temperature, Hildebrand (119) found precipitation to occur at a pH value of *ca.* 3. Similar measurements by Britton (40, 42) at 17–18°C. on solutions approximately 0.01 *N* in thorium ion indicated precipitation to begin at pH values of 3.51 for the chloride, 3.53 for the sulfate, and 3.57 for the nitrate. Bowles and Partridge (35) reported incidence of precipitation at pH 3.91 for thorium sulfate solutions and at 2.65 and 2.75 for cerium(IV) sulfate and cerium(IV) ammonium sulfate solutions, respectively, all measurements having been made with approximately 0.01 *M* solutions at 25°C. Thus, sufficient differences exist between precipitation pH values to permit separations of thorium from yttrium and the trivalent rare earth elements even if only moderately accurate pH control is maintained. Direct separation of thorium from cerium(IV) by this means appears impractical if not impossible.

Separation by alkaline precipitation was used extensively long before quantitative evaluation of pH differences was effected. The caustic alkalies and ammonia received some attention (24, 25, 220, 221), but, as is true with the rare earth elements alone (189), pH control with these highly alkaline reagents is too difficult to make their use practical. More success has attended the use of less basic metal oxides, hydroxides, and carbonates and of organic derivatives of ammonia.

Early work by de Boisbaudran (66, 67) showed that if solutions were first boiled with copper to reduce tetravalent cerium materials, thorium could be separated from the trivalent rare earth elements by precipitation with copper(I) oxide from hot solution. Removal of copper materials by hydrogen sulfide then yielded a purified thorium preparation free from rare earths. This procedure has never been widely used. Giles (95) separated thorium from the trivalent rare earth elements by treating a neutral or slightly acidic mixed nitrate solution with lead carbonate, lead ion being removed as sulfide after dissolution of the precipitated hydrous thorium oxide in acid. In addition to thorium, zirconium, cerium(IV), and iron(III) materials were found to precipitate completely, and partial precipitation of uranium, chromium(III), and aluminum was noted. Inasmuch as special precautions are necessary in the preparation of the lead carbonate, the method has assumed no large-scale importance. However, if zirconium materials have been removed and cerium(IV) materials reduced with sulfur dioxide, quantitative removal of thorium from rare earth materials may be effected in this fashion (188, 224). The use of mixed rare earth hydrous oxides and hydroxides for the precipitation of thorium and its concomitant separation from the rare earth elements has been patented (204). It has the advantage of avoiding addition of alkali and is said to be very effective (156), although zirconium, titanium, and cerium(IV) materials are precipitated as well. Barium carbonate is said to precipitate thorium and the cerium earths but not the yttrium earths from cold solution (26).

In an attempt to find specific metal oxides or carbonates for the precipitation of certain of the rare earth elements and thorium, Neish and Burns (196) compared the hydrogen-ion concentrations in 0.01 *N* nitrate solutions of lanthanum, cerium(III), cerium(IV), praseodymium, neodymium, and thorium with the hydroxyl-ion concentrations in creams of various water-insoluble oxides and carbonates at 25°C. On the basis of the relative quantities of hydrogen ion in the salt solution and of hydroxyl ion in contact with the oxide or carbonate, they predicted that:

1. Certain oxides, such as FeO and CoO, furnishing only small amounts of hydroxyl ion, would not be expected to precipitate thorium completely.
2. Other oxides, such as CdO and HgO, furnishing greater concentrations of hydroxyl ion, would precipitate thorium essentially completely.
3. Oxides and carbonates such as ZnO, CuO, PbO, $ZnCO_3$, and $PbCO_3$, furnishing still greater quantities of hydroxyl ion, would precipitate thorium and cerium(IV) completely but would not precipitate the trivalent rare earth elements.

Experimentally, complete precipitation of thorium was effected by treating thorium nitrate solution (followed by boiling or allowing to stand for several hours in the cold) with zinc oxide, cadmium oxide, lead oxide (Pb_3O_4), cuprous oxide, lead carbonate, zinc carbonate, cupric carbonate, and manganous carbonate, while only incomplete precipitation was effected with ferrous oxide, nickelous oxide, cobaltous oxide, cupric oxide, ferric oxide, and chromic oxide. The carbonates of manganese, copper, and lead gave precipitates which were easiest to handle. Cerium(IV) was precipitated in the same manner as thorium.

For the separation of thorium from the rare earth elements, Neish and Burns (196) recommended the following precipitants: lead carbonate, 60°C. for 2 hr.; cupric carbonate, cold; zinc carbonate, heated just to boiling; lead oxide (Pb_3O_4), cold; cuprous oxide, 100°C. for 1 hr.; manganous carbonate, 64°C.; and zinc oxide, cold. Precipitation of the trivalent rare earths was insignificant in all cases except with zinc oxide. For the systematic removal of thorium from the rare earth elements, prior reduction of cerium(IV) materials with hydrogen sulfide or sulfur dioxide followed by treatment in an atmosphere of carbon dioxide with either lead carbonate, zinc carbonate, cupric carbonate, lead oxide (Pb_3O_4), or zinc oxide in slight excess was recommended. The precipitated hydrous thorium oxide was then dissolved in acid, and thorium was reprecipitated as hydrous oxide free from the rare earth elements.

Separations based upon the concept of controlled pH which is implicit in the work of Neish and Burns (196) have also been effected by the use of organic derivatives of ammonia. Extensive investigations of the behavior of thorium, zirconium, lanthanum, cerium(IV), praseodymium, and neodymium salt solutions toward a variety of substituted ammonias have been reported by both Jefferson (132) and Hartwell (105). Jefferson found thorium to be precipitated quantitatively by aniline, dimethylaniline, diethylaniline, piperidine, quinoline, and pyridine and nearly quantitatively by *o*-toluidine and xylidine. Zirconium was precipitated quantitatively by all these reagents and cerium(IV) by most of them. For quantitative separation of thorium from the trivalent rare earth elements studied, Jefferson recommended the use of aniline or quinoline. Hartwell extended these observations to many other amines, both aromatic and aliphatic, and suggested the use of *p*-chloroaniline, hexamethylenetetramine, and *p*-toluidine for the removal of thorium. Other amines, such as benzidine, *m*- and *p*-bromoanilines, *p*-bromophenylhydrazine, *m*-tolylenediamine, isoquinoline, α-picoline, and tribenzylamine, were found to precipitate thorium (and zirconium) but not the rare earth elements. More alkaline amines, particularly the aliphatic derivatives, precipitated the rare earth elements as well as thorium.

The use of aniline for selective precipitation of thorium has also been recommended by Kolb (145) and Allen (2). Allen found titanium, zirconium, and cerium(IV) materials to be precipitated as well and reported hydrazine to behave in the same fashion as aniline (2). Pyridine has been used by Atanasiu (4) for the quantitative precipitation of thorium in the presence of the cerium earths, and quinoline has been suggested for the same purpose (214).

A much better reagent for the removal of thorium from the rare earth elements is hexamethylenetetramine (or hexamine). Since this material undergoes hydrolysis to ammonia in solutions containing even a small concentration of hydrogen ion, it may be used to give solutions of controlled pH. Although Ray (207) showed that both thorium and zirconium could be precipitated quantitatively by heating their aqueous salt solutions with hexamine, it remained for Ismail and Harwood (126) to apply the method to thorium–rare earth mixtures. Ismail and Harwood found the hydroxyl-ion concentration in an aqueous solution of hexamine to be sufficient, even in the presence of buffering ammonium salts, to precipitate thorium completely and leave the rare earth elements unprecipitated even at the boiling temperature. Their quantitative method for thorium estimation based upon this behavior will be discussed in detail in a later section. In the presence of much cerium, a second precipitation was required for the production of pure thorium material.

Neither acetamide (178), semicarbazide (178), succinimide (178), nor urea (50, 178) is sufficiently basic itself to precipitate thorium. However, slow decomposition of hot solutions of urea into ammonia and carbon dioxide might provide media of controlled pH suitable for separation of thorium from the rare earth elements. Although materials used by Fogg and Hess (84a) in their studies upon the separation of the yttrium earths by this means contained thorium, no record of the behavior of the thorium was reported. Extension of this and other methods involving rigid pH control should be fruitful for the selective precipitation of thorium.

(b) Separation by hydrolytic precipitation

Because of the reduced basicity of the thorium ion, salts containing rather strongly basic anions should, if soluble, be more susceptible to conversion into water-insoluble products by hydrolysis than the corresponding salts of the trivalent rare earth elements. Of the salts admitted by the basicity and solubility restrictions, the thiosulfates, azides, and nitrites have been investigated most extensively.

Separation of thorium by precipitation through hydrolysis of solutions containing thiosulfate ion is a classical procedure (22, 26, 38, 54, 89, 90, 120, 124, 162, 167, 183, 215, 224), which was apparently used first by Chydenius (59). Although Chydenius reported that treatment of a neutral or slightly acidic mixed salt solution with sodium thiosulfate precipitated thorium along with some sulfur, whereas the rare earth elements remained largely unprecipitated, he did not regard the method as completely separative. Lack of precipitation of lanthanum and didymium was verified shortly thereafter by Hermann (117, 118), and the procedure was adapted to thorium–rare earth separations by Bunsen (48) and to thorium recovery from monazite by Fresenius and Hintz (87). Witt (256) recommended several successive precipitations with warm thiosulfate followed by an oxalate extraction for the complete purification of thorium. The oxalate and thiosulfate procedures were found to be about equally efficient by Hintz and Weber (122), Drossbach (77), and Benz (16). Various other workers have also employed the method to advantage (94, 133, 178). In its present form, the procedure involves boiling after addition of thiosulfate (120, 183, 224), but since complete separation is not effected in a single step, the procedure must be repeated several times. It is, therefore, of but limited value for the rapid, large-scale separation of thorium from yttrium and the rare earth elements, although, if carefully controlled, it can effect quantitative separation (120). Although early investigators considered the precipitate to be thorium thiosulfate (59, 117, 118), more recent work has shown it to be the hydrous oxide admixed with sulfur (224). Both scandium and zirconium are precipitated with thorium in this procedure (224).

Dennis and Kortright (72, 73) reported that addition of 0.3 per cent sodium or potassium azide solution to a cold solution containing thorium and rare earth metal nitrates, followed by boiling, precipitated thorium quantitatively and effected its separation from lanthanum, cerium, and didymium. Further work by Dennis (70, 71) showed separation from lanthanum to be quantitative. In this procedure, thorium is precipitated as hydrous oxide because of extensive hydrolysis of the azide ion (119). In spite of the excellence of the results obtained by Dennis (and Kortright), Wyrouboff and Verneuil (261) found the procedure to be ineffective in the presence of cerium. Because of the cost of the reagent and the hazards attending its use, the method has never been favorably received.

Precipitation of thorium by hydrolysis of nitrite solutions has been reported (11), and an extension of the classical nitrite procedure (189) would be expected to concentrate thorium in the least basic fractions. Efficient separation of thorium in this fashion would be highly improbable because of difficulty in sufficiently accurately controlling the pH.

Precipitation of thorium as basic acetate by boiling thorium salt solutions with excess sodium acetate was found by Haber (103a) to yield thorium free from didymium. Although recommended as very effective by Mingaye (188), this method is too expensive to be of general use.

(c) Separation by miscellaneous procedures

The steady increase in pH in the vicinity of the cathode during electrolysis of aqueous nitrate solutions was used by Dennis and Ray (73a) for the rapid concentration of thorium from synthetic mixtures with the rare earth elements and from monazite extracts. The weakly basic thorium precipitated in the first fractions, and in a single step increases in thorium content from 14.76 per cent to 78.63 per cent and from 5 per cent to 52 per cent were effected. Although complete separation from the rare earth elements was not reported, the success which has attended fractional separation of the latter elements by this means (189) suggests its even greater effectiveness in the removal of thorium.

Use of chlorine and caustic alkali has been proposed (220, 221), the more basic hydrous oxides and hydroxides of yttrium and the trivalent rare earth elements being more soluble than hydrous thorium oxide. However, the procedure offers no advantages and is, of course, incapable of separating thorium from cerium. Some separation may be effected by treatment of the mixed oxides with acids, since thorium oxide is much less soluble than the others (140), but such separation is only fractional in character. Concentration of thorium in the least basic fractions in the nitrate fusion process (189) has been used to advantage for the removal of thorium from rare earth mixtures (158a, 197, 239), although separation from the least basic members of the rare earth series by this means is incomplete (23).

3. Methods dependent upon differences in solubilities of particular compound types

Separation of thorium from the rare earth elements by solubility differences may be effected by preferential precipitation, by preferential dissolution of precipitated materials, or by crystallization. Of proposed procedures based upon these principles, those involving crystallization are most apt to be fractional in character. Because of the difficulties imposed by the removal of phosphate, much of the investigative work which has been carried out has been directed toward removal of thorium by precipitation from solutions which are sufficiently acidic to prevent precipitation of phosphates of yttrium and the trivalent rare earth elements. In all methods embracing these general principles, complication by cerium(IV) compounds is to be expected.

(a) Precipitation from strongly acidic solutions

Most common of such procedures are those involving phosphates of various types. These procedures are all dependent upon precipitation of the thorium compounds from solutions which are too strongly acidic to permit precipitation of the corresponding derivatives of the trivalent rare earth elements. Britton (44) has reported precipitation from thorium chloride solutions containing phosphate at pH 2.72, but in the experience of the authors, precipitation occurs at even lower pH values. The true nature of the phosphate-containing precipitate is doubtless dependent upon the total acidity and previous treatment of the solution from which it is formed, but it appears not unlikely that the pyrophosphate is the common product (203). Removal of thorium by reduction of acidity through dilution or addition of ammonia or magnesium oxide from extracts obtained by sulfuric acid treatment of phosphate minerals such as monazite or xenotime is a classical procedure (25, 54, 124, 147, 163, 205, 224), variations of which have been covered by numerous patents (e.g., 19, 20, 100). Separation in this fashion is not complete, for complete removal of the thorium always results in its contamination by small amounts of the rare earth elements. The convenience of the procedure for direct recovery of relatively pure thorium from its most important sources, however, renders the method of extreme technical importance.

Direct precipitation of thorium with alkali pyrophosphate from solutions approximately 0.3 *N* in hydrochloric acid has been recommended by Carney and Campbell (49, 52) as a particularly efficient method of separation. While cerium (IV) and zirconium pyrophosphates are also precipitated under these conditions, those of the trivalent rare earth elements are not. The method is based upon early observations on the insolubility of the thorium derivative, $ThP_2O_7 \cdot 2H_2O$, by Cleve (62), and is sufficiently accurate to be adaptable to the quantitative estimation of thorium in mixtures (52).

Precipitation of thorium hypophosphate, $ThP_2O_6 \cdot 11H_2O$, from solutions containing sizable quantities of free acid was first recommended by Wirth (252) as a means of separation, since under such conditions yttrium and the rare earth elements are not precipitated. At almost the same time, the same procedure was reported by Koss (151), who recommended precipitation from 6 per cent hydrochloric acid solution, and by Rosenheim (209), who suggested generation of hypophosphoric acid within the salt solution by anodic oxidation of a copper(II) phosphide electrode. The basic features of the method have been patented (74, 152), and while either hypophosphoric acid or its alkali metal salts may be used, the former has been recommended for use in a sulfate medium (254) because of the possible precipitation of double sulfates of the cerium earths by the latter. In a more recent publication (107), the use of a 10 per cent hydrochloric acid medium has been suggested. Hypophosphates of titanium, zirconium, and cerium(IV) also precipitate from acidic solutions (107, 252), but interference from these materials may be eliminated by methods already discussed. Recovery of thorium may be effected by ultimate precipitation as oxalate after decomposition of the precipitate with sodium hydroxide (252) or mixed sulfuric and fuming nitric acids (224). Use of the hypophosphate method offers no apparent advantages over use of the pyrophosphate and has the disadvantage of requiring a less common and more expensive reagent.

Ryan has recommended both sodium metaphosphate (211) and disodium ammonium phosphate (212) as efficient precipitants for the removal of thorium from acidic solutions containing rare earth materials, but neither material has been widely used. It is not improbable that an adaptation of Willard and Freund's hydrolytic phosphate method (249) might be useful for at least the small-scale separation of these elements.

A procedure depending upon the precipitation of thorium as fluosilicate from boiling solutions containing large excesses of mineral acids and the lack of precipitation of the rare earth elements under the same conditions was patented by Rosenheim, Meyer, and Koppel (210). While this method has not been used extensively, it appears to yield excellent results and should be applicable to fairly large-scale separations. Recovery of thorium from the precipitate is effected by conversion to sulfate with sulfuric acid (210).

A convenient and precise method of effecting this separation on a laboratory scale is the iodate procedure of Meyer and Speter (186). Precipitation of thorium as iodate is reported to be complete even if the solution contains 40 per cent by volume of concentrated nitric acid, providing a large excess of potassium iodate is used as precipitant. Under these conditions the trivalent rare earth elements are not precipitated, but scandium, zirconium, and cerium(IV) are (39, 180). Prior reduction with sulfur dioxide renders separation from cerium complete (180), and scandium and zirconium may be removed as previously outlined. Recovery of thorium is effected by reduction of the iodate with sulfur dioxide and subsequent precipitation with oxalic acid. While the method has proved very effective (137, 139, 180, 186, 191) and has been recommended very highly (26, 38, 55, 120, 124, 162, 167, 184, 215, 224), precipitation of thorium is complete only in the presence of a comparatively large excess of iodate because of the measurable water solubility of the compound (92). Because of the quantities and high costs of the reagents involved, the method shows no promise for large-scale separations, but it does have the advantages of working in the presence or absence of phosphate and of being quantitative in nature (26, 38, 58, 92, 120, 156, 234). Detailed instructions for its application are to be found in the listed references.

(b) Precipitation from weakly acidic or neutral solutions

In 1885, both Cleve (64) and de Boisbaudran (68) reported precipitation of thorium by means of hydrogen peroxide. Although Kossman (153) employed this reaction for the separation of thorium, the first comprehensive studies were made by Wyrouboff and Verneuil (258, 259, 260, 262). As recommended by these authors, the method amounts usually to treatment of warm (60–80°C.), neutral or slightly acidic, nitrate solutions containing ammonium nitrate with 3–10 per cent hydrogen peroxide, although preliminary separations may be effected by use of the more basic barium peroxide (262). While solutions containing as little as 0.001 per cent of thorium will yield precipitates under these conditions (22, 167), removal of thorium from rare earth mixtures is complete only if the quantity of thorium is comparatively small (167). Cerium(IV), titanium, and zirconium materials are also precipitated by hydrogen peroxide, but a second precipitation is usually sufficient to remove cerium. While the method is satisfactory for the removal of the bulk of the rare earth elements from thorium, quantitative separation can be effected only if the operation is repeated numerous times. Under such conditions, the method becomes tedious and costly. Benz (16) regarded the hydrogen peroxide procedure as the equal of the thiosulfate method, and in modified form it has been patented for large-scale operation (60, 61). Early workers formulated the precipitated peroxy compounds variously as $Th_4O_7 \cdot SO_3$ (64) and $Th_4O_7 \cdot N_2O_5$ (258), but in the light of more modern evidence it is probable that $Th_2O_7 \cdot 4H_2O$ is formed (216).

A number of other precipitants have been suggested for use under these conditions, because thorium compounds are commonly less soluble than the corresponding compounds of yttrium and the rare earth elements. The majority of these materials give only fractional separations and cannot be used for the quantitative removal of thorium in a single operation. As a consequence, they are of no technical importance and are useful only for the laboratory concentration of the element. Among these precipitants are sodium acetate from acetic acid solutions (25, 163), guanidine carbonate (51), hydrofluoric acid or soluble fluoride (75), ammonium vanadate (194, 195), ammonium molybdate (179), sodium tungstate (194, 195), and potassium chromate (172, 192, 223) or dichromate (223). Original reports (179) of the completeness of the molybdate separation have been questioned recently (10a), but it is probably the most effective of those listed.

Purification of thorium compounds by precipitation as double sodium sulfate (21) or double potassium sulfate (33, 161) is a well-known procedure. That the thorium compounds are less soluble than the corresponding compounds of the cerium earth elements is the basis for separational methods depending upon fractional precipitation of these materials (63, 127, 128, 228). James (127, 128) has suggested removal of thorium from the yttrium earths by this means, with subsequent removal of coprecipitated cerium earths by the ammonium carbonate or hydrogen peroxide procedures.

The thorium salts of many organic acids are also markedly less soluble than corresponding salts of yttrium and the rare earth elements. The relative utilities of a number of such acids in effecting thorium–rare earth separations are summarized in table 1. Only fumaric (178), *m*-nitrobenzoic (194, 195), sebacic (222), phenoxyacetic (205), phenylarsonic (208), quinaldic (80), and alizarin-3-sulfonic (15) acids and 8-hydroxyquinoline (115) may be regarded as sufficiently effective to merit use. However, all of these reagents are costly and are therefore limited in their use to laboratory operations. Zirconium is also precipitated by the majority of these materials. Use of oxalic acid cannot be regarded as an effective means of separation, for although thorium oxalate is less soluble in acidic solutions than the oxalates of the other materials (253), solubility differences are insufficient to give anything but fractional separations.

The fumaric acid procedure of Metzger (178) entails use of a saturated solution of the reagent in 40 per cent ethanol and addition of 40 per cent ethanol by volume to the thorium–rare earth salt solution. It has been applied successfully to the removal of thorium from monazite (157). The isomeric nitrobenzoic acids are all effective in precipitating thorium, but the meta acid is preferred (194,

TABLE 1

Organic acids for removal of thorium from rare earth elements

REAGENT	REMARKS	REFERENCES
Alizarin-3-sulfonic acid	Precipitates thorium and scandium but not trivalent rare earth elements	(15)
Anisic acid	Only fair separation	(205)
Aspartic acid	Only fair separation	(205)
Benzoic acid	Incomplete separation	(146, 194, 195)
Cinnamic acid	Incomplete separation	(146, 178)
Citric acid	Ineffective	(194, 195)
8-Hydroxyquinoline	Effective at controlled pH	(115, 169)
Fumaric acid	Precipitates thorium and zirconium but not trivalent rare earth elements	(178)
Gallic acid	Ineffective	(194, 195)
Linoleic acid	Ineffective	(194, 195)
Maleic acid	Ineffective	(178)
Mucic acid	Only fair separation	(205)
m-Nitrobenzoic acid	Precipitates thorium but not trivalent rare earth elements	(194, 195)
Oleic acid	Ineffective	(194, 195)
Oxalic acid	Ineffective	(253)
Oxyisophthalic acid	Ineffective	(194, 195)
Phenoxyacetic acid	Precipitates thorium but not trivalent rare earth elements	(205)
Phenylarsonic acid	Precipitates thorium and zirconium but not trivalent rare earth elements	(208)
Phthalic acid	Ineffective	(178)
Picric acid	Ineffective	(178)
Picrolonic acid	Precipitates thorium and trivalent rare earth elements	(112)
Pyrotartaric acid	Only fair separation	(205)
Quinaldic acid	Precipitates thorium, zirconium, and uranium but not trivalent rare earth elements	(80)
Salicylic acid	Incomplete separation	(146, 194, 195)
Sebacic acid	Precipitates thorium, but not trivalent rare earth elements	(222)
p-Toluic acid	Ineffective	(194, 195)

195). Its effectiveness is said to equal that of fumaric acid, although two precipitations from neutral solution are required for complete separation (194, 195). Many investigators have employed this method to advantage (3, 96, 146, 172). Use of sebacic acid appears to be equally effective in nearly neutral boiling solutions (222), although it is complicated by precipitation of rare earth sebacates at high sebacate-ion concentrations, e.g., with ammonium sebacate (248), and by precipitation of cerium when present in high concentrations (136). In the presence of cerium, use of ethanol solutions of sebacic acid has been recommended (136). The sebacic acid procedure has given favorable results in the hands of several investigators (136, 229, 230), and its use has been patented (144). The phenylarsonic acid procedure (208) depends upon the relative insolubility of the thorium compound in acetic acid–ammonium acetate mixtures. The difficulty of removing cerium and the necessity for double precipitation complicate this procedure (138). Phenoxyacetic (205), alizarin-3-sulfonic (15), and quinaldic (80) acids all appear promising, especially the latter since separation from zirconium may also be effected from cold solutions. Use of 8-hydroxyquinoline as a precipitant has been confined largely to the estimation of thorium (17, 113, 115), but since Mannelli (169) has established pH differences for the precipitation of thorium and the rare earth elements with this reagent, separations at controlled pH values might be expected. Precipitation of the thorium compound is said to be complete at pH 4.4 (102), while 8-hydroxyquinoline derivatives of the trivalent rare earth elements are completely precipitated at pH values above 6 (92). Berg and Becker (18) effected complete separation of thorium from cerium(III) by first precipitating the thorium derivative from a solution containing 2.5 per cent of free acetic acid by volume and then precipitating the cerium(III) derivative from the filtrate by adding ammonia. Further work with this reagent is indicated.

(c) Fractional crystallization

Because of the existence of shorter and more precise methods, fractional crystallization procedures are of little or no importance for these separations. Of the several which have been suggested, the sulfate procedure is most important since it may be employed for the removal of small amounts of yttrium and cerium earth materials from thorium compounds (163). Based upon the fact that the solubility of hydrated thorium sulfate in water decreases more rapidly as the temperature is increased than do the solubilities of the rare earth metal sulfates (158, 158a, 197, 256), the method usually amounts to dissolving the impure sulfate in ice water and crystallizing the octahydrate by warming to 20°C. (163). Koppel and Holtkamp (147) have recommended crystallization from hydrochloric acid medium as requiring less careful temperature control. Two or three repetitions are needed to yield a pure product, and the method is particularly useful where the cerium content is low (251). Greater solubility differences are said to exist with the ethyl sulfates than with the sulfates alone (155).

Fractional crystallization of the double ammonium nitrates as suggested by

Witt (255) offers no advantages. A method of potential small-scale utility involves precipitation of practically all of the cerium earth elements as double thallous sulfates, followed by crystallization of a double thorium–thallous sulfate upon evaporation of the filtrate by one-third (83). Thorium material so obtained is said to be free from rare earths and zirconium, a double zirconium–thallous sulfate crystallizing only upon further evaporation. Crystallization of the mixed acetates, followed by selective leaching of rare earth metal acetates away from the less soluble thorium acetate, has been reported to be effective (25).

4. Methods dependent upon other differences in properties

Procedures dependent upon the greater covalent characteristics of thorium compounds should be effective for removal of this element from yttrium and the rare earth elements. But little is known about such procedures at the present time, although removal of thorium from cerium by volatilization of its chloride at 700–800°C. has been reported (34). On this basis, preferential extraction of thorium compounds from aqueous solution into organic solvents might be expected. Such a method should be of technical importance because of its applicability as a continuous process.

Another procedure which is showing some promise involves differences in rates of reaction of thorium and rare earth metal ions with cation exchangers (169a).

5. Summary

But few of the outlined procedures are adaptable to the large-scale separation of thorium from yttrium and the rare earth elements. Technically, the major part of the available thorium is recovered from monazite, in which mineral the ratio of thorium to rare earth elements is quite small. The simplest, most efficient, and most widely used procedure entails precipitation of a phosphate of thorium by careful reduction of acidity of the sulfuric acid extract of the mineral. Subsequent treatment by other procedures is essential for the preparation of thorium compounds completely free from the rare earth elements and yttrium. Thus, after removal of phosphate by oxalate precipitation or fusion with alkalies, final purification may be effected through the thiosulfate, peroxide, oxalate, sebacic acid, or sulfate crystallization procedures, all of which are tedious and somewhat costly. For laboratory-scale separations, use of more precise but more expensive methods, such as those involving iodate, *n*-nitrobenzoic acid, etc., is desirable. Ultimate separations from zirconium, cerium(IV), and the least basic members of the yttrium earth series are usually necessary for final purification. Methods which are at the same time rapid, quantitative, and inexpensive have yet to be developed.

IV. QUANTITATIVE ESTIMATION OF THORIUM

Exact methods for the quantitative estimation of thorium are of interest because of the growing importance of the element in the production of catalysts and alloys and in the investigation of nuclear phenomena. While accurate estimation of the element in its pure compounds or in the absence of materials such as uranium, zirconium, scandium, yttrium, and the rare earth elements is simple, procedures for use in the presence of these elements are often involved and complicated by interferences. Such procedures may take either of two forms; namely, prior removal of the interfering elements or determination of thorium in their presence. Because of difficulties attending removal of interfering elements (see Section III), reliable procedures of the second type are highly desirable. Unfortunately, adequate methods of this type are limited in number. Proposed procedures of all types may be classified conveniently as gravimetric, titrimetric, radiometric, and miscellaneous. Detailed summaries of quantitative procedures appear in many references (10a, 26, 38, 54, 89, 109, 110, 120, 134, 163, 174, 176, 183, 215, 224, 232, 233, 234, 241).

A. GRAVIMETRIC ESTIMATION

Almost without exception, gravimetric procedures involve ultimate weighing of thorium as the ignited oxide. Commonly, this is preceded by a separational procedure of the type already discussed (see Section III) to remove interfering materials. In most of the methods to be outlined below, the principles already discussed under separations in Section III are apparent, for separational procedures and those for quantitative estimation are often essentially the same. An excellent, albeit brief, review of existing gravimetric procedures has been published recently by Jüstel (134).

1. Estimation as oxide

Estimation as oxide ordinarily entails precipitation as hydrous oxide or oxalate, since these precipitates may be ignited directly. Because of the volatility or instability of ammonium salts at elevated temperatures, aqueous ammonia is preferable to the more difficultly removable fixed alkalies as a precipitant for hydrous thorium oxide. Precipitation from 5–10 per cent ammonium nitrate solution, followed by digestion on the steam bath and washing with warm 5–10 per cent ammonium nitrate solution containing 2 per cent ammonia, has been recommended as yielding quantitative results (109).

As substitutes for ammonia, many organic amines have been suggested (105, 132). Although many such compounds offer no advantages over ammonia, certain of them (see Section III) precipitate thorium without affecting yttrium and the rare earth elements. Thus, aniline (2, 145), pyridine (4), quinoline (214), and phenylhydrazine (2) have all been used for the estimation of thorium in the presence of rare earth elements. However, these precipitants appear too uncertain in their behavior to have merited widespread use, and interference from zirconium, titanium, and cerium(IV) materials is to be expected. Perhaps the best results have been obtained with hexamethylenetetramine. According to Ismail and Harwood (126) thorium is completely precipitated and quantitatively removed from the rare earth elements when a 10 per cent solution of the amine is added to a mixed salt solution containing about 5 per cent of ammonium chloride and the whole is warmed to 30°C. A second precipitation with the amine prior to ignition is recommended for complete removal of cerium, but under these conditions results comparable with those obtained with the classical thiosulfate procedure were reported. The method may be applied to the direct determination of thorium in monazite if preceded by two oxalate precipitations to remove zirconium (126), but its application to mixtures rich in the yttrium earth elements should be investigated further (134).

The principle of separation through controlled pH by use of metal oxides or carbonates as precipitants may also be applied to the estimation of thorium in the presence of yttrium and the rare earth elements. The copper(I) oxide procedure of de Boisbaudran (66, 67) is effective for the estimation of thorium under these conditions if preceded by boiling with copper to reduce interfering cerium(IV) compounds. Equally effective is the lead carbonate procedure of Giles (95), also if preceded by reduction of cerium(IV) materials. Reagents recommended by Neish and Burns (196), such as the carbonates of copper, zinc, and manganese and the oxides of zinc and lead (i.e., Pb_3O_4), may be expected to behave in the same fashion. Use of any of these precipitants must presuppose prior removal of zirconium as well as reduction of cerium(IV) and must be supplemented by removal of the introduced metallic ion. Ultimate precipitation of thorium as hydrous oxide or oxalate ordinarily completes the determination.

The principle of controlled pH is also implicit in the hydrolytic selective precipitation of hydrous thorium oxide with alkali metal azides (72, 73). Although quantitative separation of thorium from lanthanum, cerium, and didymium by this means has been claimed (70, 71, 72, 73), Wyrouboff and Verneuil (261) reported inaccuracies in the presence of cerium, and the method is of no present importance (134).

Precipitation as oxalate is most commonly effected by treatment of a nearly boiling thorium salt solution, containing not more than 4–5 per cent by volume of mineral acid (usually hydrochloric or nitric) (109, 114, 120), with saturated oxalic acid solution (26, 38, 109, 114, 120, 215). Filtration after a period of standing of at least 6 hr. (38) may then be followed by washing with warm, dilute oxalic acid solution and ultimate ignition at 950–1100°C. (109, 114, 120). In this form, the method is applicable to micro determinations as well as macro (114). No separation from the rare earth elements or yttrium is effected, but the method may be applied to the estimation of thorium in the presence of zirconium because of the non-precipitation of the latter element. Because of the marked solubility of thorium oxalate in strongly acidic solutions (106), reasonably rigid acidity control is essential for quantitative recovery. Owing to its solvent effect upon thorium oxalate, ammonium oxalate is not a suitable precipitant. Quantitative methods for thorium based upon extraction of its oxalate from a mixed oxalate precipitate in this fashion (77, 97, 98, 99, 121, 122, 178) are ineffective because of incompleteness of the separation (16, 26).

Estimation of thorium as oxide in tungsten–thorium mixtures by volatilizing the tungsten away by heating in a current of air and chloroform vapor and weighing the residue has been recommended (218).

2. *Estimation in strongly acidic solutions*

The direct estimation of thorium in solutions containing comparatively large quantities of free mineral acids is of considerable importance, because under such conditions prior removal of phosphates is unnecessary. Furthermore, such media are advantageous because of the rather sizable solubility differences noted between compounds of thorium and compounds of rare earth elements. As a consequence, these methods are often directly applicable to analyses of monazite and other phosphate minerals. Because they require fewer manipulations than do many other methods, such procedures are said to be rapid. The term is to be used advisedly.

(a) The iodate procedure

Perhaps the most highly recommended procedure for use under these conditions is the iodate procedure of Meyer and Speter (186). Indeed, Kaufmann (139) recommended it as being the simplest and most accurate of seven commonly used methods, including the gravimetric sebacic acid and volumetric molybdate procedures. Depending as it does upon the insolubility of thorium iodate in solutions containing excess iodate and up to 40 per cent of nitric acid by volume as contrasted with the solubilities of iodates of the trivalent rare earth metals under similar conditions, the method is directly applicable to mixtures containing these elements. Since cerium(IV) iodate is also precipitated (39, 180), prior reduction with sulfur dioxide (180) or hydrogen peroxide (58) is necessary. In its usual form, the method then consists of precipitation of the iodate from a cold solution, washing with a solution containing potassium iodate and nitric acid, dissolution in excess nitric acid, reprecipitation as iodate, dissolution in hydrochloric acid by reduction of iodate with sulfur dioxide, precipitation of the hydrous oxide with ammonia, dissolution in hydrochloric acid, and ultimate precipitation of ignitable thorium oxalate (26, 120, 186, 224). Final treatment with oxalic acid removes any titanium or zirconium, but scandium must be removed by previous precipitation (180). In this form the method has yielded excellent results, particularly in the analyses of monazite (92, 137, 138, 156, 186) and cyrotolite (191). It is said to be a standard procedure in the monazite industry (134, 156). It has the advantage of comparative rapidity (186) and is also adaptable to micro determinations (139). However, a number of difficulties are encountered in the handling of the precipitated iodate (92). Some of these may perhaps be obviated by using centrifugal separation (156). Because of the marked solubility of thorium iodate in the absence of iodate ion (92), large quantities of this ion are necessary for both precipitation and washing.

In a recent publication, Chernikhov and Uspenskaya (58) have reported precipitation of thorium as $4Th(IO_3)_4 \cdot KIO_3 \cdot 18H_2O$ and of cerium(IV) as $2Ce(IO_3)_4 \cdot KIO_3 \cdot 8H_2O$ from solutions containing excess nitric acid and about 5 per cent excess potassium iodate by weight. Although precipitation was carried out in the usual fashion, ultimate removal of nitric acid and excess iodate was effected by washing the precipitates with ethanol. Prior reduction of cerium with peroxide permitted quantitative precipitation of thorium free from cerium, the cerium then being recovered as iodate after bromate oxidation. While this modification is adaptable to the gravimetric estimation of cerium and thorium, it is chiefly useful as extended to a volumetric procedure.

(b) The hypophosphate procedure

Selective precipitation of thorium as hypophosphate from boiling, strongly acidic solutions (151, 209, 252) is useful for the quantitative estimation of the element in the presence of the rare earth elements and yttrium. For rough determinations, Rosenheim (209) recommended ignition of the hypophosphate to weighable pyrophosphate, but lack of constancy in composition of the ignition product (107, 209) requires decomposition of the precipitated compound with either caustic alkali (252) or mixed sulfuric and fuming nitric acids (224) followed by precipitation as oxalate for accurate results. Final precipitation with oxalic acid serves also to remove any precipitated titanium and zirconium, and interference from cerium(IV) may be obviated by reduction with hydrogen peroxide. Since precipitation from sulfate media may be complicated by separation of double alkali metal sulfates with the rare earth elements (254), use of chloride or nitrate media is preferred. Detailed studies by Hecht (107) have indicated best results from the method when precipitation is effected from 10 per cent hydrochloric acid solution after hydrogen peroxide reduction and is followed by successive fusions with alkali carbonates and pyrosulfates and ultimate oxalate precipitation. In the opinion of Jüstel (134), the hypophosphate procedure is more suited to the qualitative detection of thorium and requires verification in the presence of cerium and the other rare earth elements before it can be considered as quantitative.

(c) The pyrophosphate procedure

The pyrophosphate procedure of Carney and Campbell (52) is said to give excellent results (26, 120), although it is rather tedious of operation. As commonly employed (26, 52, 120), the method consists in precipitating thorium with sodium pyrophosphate from boiling solutions 0.3 N in hydrochloric acid. Under these conditions, the trivalent rare earth elements remain unprecipitated, but zirconium, titanium, and cerium(IV) compounds contaminate the thorium material. Either digestion of the precipitate plus filter paper with sulfuric acid and ammonium perchlorate or treatment with fuming nitric acid (53) is recommended, thorium being recovered by precipitation with sodium hydroxide. Dissolution of the precipitated hydrous oxide, reduction of cerium(IV) with sulfur dioxide, a second pyrophosphate precipitation and Kjeldahl digestion, and ultimate precipitation with oxalic acid yield pure thorium materials. Insufficient acid is said to prevent complete precipitation through formation of soluble $Na_4Th(P_2O_7)_2 \cdot 2H_2O$ (26) and may permit precipitation of compounds of the rare earth elements. The method is reported to be successful for routine analysis of monazite (26).

3. *Estimation in weakly acidic or neutral solutions*

Procedures suited to these media are commonly less clean-cut than those applicable to strongly acidic solutions, because solubility differences between compounds of thorium and compounds of rare earth metals are less well defined. Prior removal of phosphate is of course necessary and is usually effected by precipitation with oxalic acid. Ultimately, the mixed oxalates are converted to nitrates either directly by action of fuming nitric acid or indirectly by ignition to oxides and dissolution in the acid, excess acid being removed by evaporation. The majority of the methods listed by van Nieuwenburg *et al.* (241) and by Wenger and Duckert (247) are applicable to such solutions.

(a) The thiosulfate procedure

A favorite classical procedure (26, 38, 120, 167, 215, 224), the thiosulfate procedure is still fairly widely used (134), in spite of its tedious nature, for gravimetric estimation of thorium in the presence of yttrium and the rare earth elements. The method was but little used for analytical purposes until after the researches of Fresenius and Hintz (87) in 1896. Further work by Witt (256), Hintz and Weber (121, 122), Drossbach (77), Metzger (178), Benz (16), and Johnstone (133) developed the method into its present form (26, 120, 167, 224). The recommended procedure entails slow addition of sodium thiosulfate solution to the boiling mixed salt solution, followed by dissolution of the precipitated hydrous thorium oxide in hydrochloric acid to separate it from sulfur and ultimate precipitation as oxalate. Complete removal of the rare earth elements, especially if appreciable quantities of the yttrium group are present or if the ratio of rare earth elements to thorium is large, is difficult (77), and in practice three or four precipitations with thiosulfate are required (16, 178). Simultaneous precipitation of aluminum, titanium, zirconium, and scandium occurs. The first three elements are removed in the final oxalate precipitation, but removal of scandium must be effected by some procedure such as Meyer and Goldenberg's tartrate (182) method. In spite of the difficulties inherent in this determination, it has been used widely for routine analysis (26, 134), for it yields accurate final results.

(b) The peroxide procedure

The peroxide procedure of Cleve (64) and de Boisbaudran (68), as modified by Wyrouboff and Verneuil (258, 259, 260, 262), was shown by Benz (16) to be suited to the quantitative estimation of thorium in the presence of the rare earth elements. Benz's procedure, which is essentially that given in later summaries (26, 120, 163, 167, 185, 224), amounts to precipitation of a neutral nitrate solution, containing ammonium nitrate and heated to 60–80°C., with 3 per cent hydrogen peroxide, followed by washing with ammonium nitrate solution, reprecipitation to remove traces of cerium, and ultimate ignition to oxide. Although early workers noted decrepitation in direct ignition of the peroxy compound and preferred destruction of the peroxide with iodide in acid and ultimate precipitation of hydrous thorium oxide prior to ignition (258), both Benz (26) and Borelli (27) obtained precipitates which settled rapidly and could be ignited without difficulty when ammonium chloride or nitrate was present. Complete separation of thorium from the rare earth elements is difficult by the peroxide procedure, and several repetitions are usually necessary. Cerium appears to coprecipitate more extensively from chloride media than from nitrate (224). Some improvement may be effected by a preliminary precipitation of all the thorium and 20–30 per cent of the rare earth elements with barium peroxide and a subsequent ammonium oxalate extraction before final precipitation with hydrogen peroxide (262). Best results are obtained when the ratio of thorium to the rare earth elements is reasonably large and when the total amount of thorium present is not more than 0.5 g.

Although not a method now in common use, largely because it is tedious, the peroxide procedure has been employed to advantage in the analysis of many thorium-containing minerals such as monazite (82, 246, 250); euxenite, polycrase, and samarskite (82); bastnasite (1); and uranite (108), the last microchemically.

(c) Procedures involving organic acids

While many organic acids yield insoluble thorium salts, only comparatively few are adaptable to use in the estimation of the element. The utility of a number of these acids in selectively precipitating thorium from its mixtures with rare earth elements has been indicated in table 1. In the discussion which follows, only those materials which have been shown to be definitely useful are considered. Although predominantly basic in character, 8-hydroxyquinoline is also included because in its thorium derivative an essentially acidic hydrogen is replaced.

(*1*) *Fumaric acid:* Precipitation of thorium from hot solutions containing 40 per cent ethanol by volume with a saturated solution of fumaric acid in 40 per cent ethanol was recommended by Metzger (177, 178) for the quantitative estimation of thorium. Although zirconium, silver, mercury, and erbium were found to interfere, a second precipitation removed any coprecipitated rare earth elements. Ignition of the precipitate in oxygen gave a weighable oxide. Comparative studies by Metzger (178) indicated the method to be as reliable as either the thiosulfate or the ammonium oxalate procedure in the presence of rare earth elements and to be much more rapid. Although used successfully by Kress and Metzger (157) for the determination of thorium in monazite, the fumaric acid procedure has not been widely applied, largely because it is still too time consuming.

(*2*) *m-Nitrobenzoic acid:* Estimation of thorium through precipitation at 60–80°C. with *m*-nitrobenzoic acid and ultimate ignition to the weighable oxide was recommended by Neish (193, 194, 195) as being the equal of the fumaric acid procedure. As with fumaric acid, a second precipitation is necessary to free the product completely from rare earth elements. In the hands of Kolb and Ahrle (146) and McCoy and Ross (172) the method has yielded excellent results, and both Ashman (3) and Girotto (96) have applied it successfully to the estimation of thorium in minerals. Use of *m*-nitrobenzoic acid or fumaric acid seems to be a matter of choice.

(*3*) *Sebacic acid:* Smith and James (222) recommended treatment of a boiling salt solution with an excess of a hot, nearly saturated solution of sebacic acid as a means of quantitatively precipitating thorium free from the rare earth elements. The voluminous precipitate settled rapidly and could be ignited directly to oxide. No interference by the rare earth elements was found, but since ammonium sebacate will precipitate these elements as well as thorium (248), it is obvious that the total acidity must not be too low. Kaufmann (136) reported coprecipitation of cerium when that element was present in comparatively large quantities and suggested an alcoholic solution of sebacic acid as precipitant, with precipitation being repeated until a white product is obtained. Comparative studies by Kaufmann (139) on a number of procedures indicated sebacic acid to give reliable results, provided preliminary isolation of thorium and the rare earth elements had been effected. The sebacic acid procedure must be ranked with those employing fumaric and *m*-nitrobenzoic acids. Approximately 0.2 g. of thorium may be determined in this fashion (174).

(*4*) *Phenylarsonic acid:* Precipitation with 10 per cent phenylarsonic acid from boiling solutions containing definite quantities of acetic acid and ammonium acetate was recommended by Rice, Fogg, and James (208) for the estimation of either thorium or zirconium. Since the precipitate could not be ignited directly, dissolution in hydrochloric acid and ultimate precipitation as oxalate were found necessary. No separation of thorium from zirconium could be effected except by repeated precipitations, but two precipitations were found to remove cerium and the other rare earth elements, the phenylarsonates of these materials being soluble in the acetic acid–ammonium acetate buffer. Results comparable with those obtained with the pyrophosphate procedure were reported for the analysis of monazite. Kaufmann (138), however, found the procedure to offer no advantages in time or precision and noted considerable interference from cerium(IV). A single precipitation carried down some 90 per cent of the cerium (138), and its removal depended upon differential solubility in hydrochloric acid rather than in the buffer. Since the precipitation of thorium was found to be incomplete in the presence of hydrochloric acid, it is apparent that rigid pH control is necessary in the method. Although cited as suitable by Prodinger (206), use of phenylarsonic acid is of doubtful importance.

(*5*) *Picrolonic acid:* Quantitative precipitation of thorium as picrolonate, $Th(C_{10}H_7N_4O_5)_4 \cdot H_2O$, has been recommended by Hecht and Ehrmann (112) for the direct quantitative estimation of thorium in either macro or micro quantities. Direct weighing of the yellow precipitate after air drying gave excellent results, the low thorium content (17.82 per cent) being highly advantageous. Precipitation was effected by treating boiling nitrate solutions containing 3 per cent acetic acid by volume (final volume) with picrolonic acid solution, but the method could not be applied to the determination of thorium in the presence of the rare earth elements, lead, or calcium. Precipitation in the presence of ammonium salts or excess acid was incomplete. According to Tanii, Hosimuja, and Ikeda (226), precipitation of thorium picrolonate is best effected in the pH range 2–3.2. The method is apparently an excellent one in the absence of the rare earth elements (109, 142, 143, 206) and is adaptable to volumetric determinations. On a macro scale, determinations are accurate to 0.1 g. (174).

(6) 8-Hydroxyquinoline: Quantitative determination of thorium by precipitation with 8-hydroxyquinoline (oxine) from a hot solution containing about 2.4 per cent acetic acid by volume was first reported by Hecht and Reich-Rohrwig (115). These authors found precipitation at 50°C. to yield a yellow product which changed to a more crystalline red material at 70°C. and reported excellent analytical results when the final precipitate was dried at 170°C. before being weighed. In an important paper, Frere (86) pointed out that the yellow material corresponded to $Th(C_9H_6ON)_4$, while the red compound amounted to $Th(C_9H_6ON)_4 \cdot C_9H_7ON$. The latter material was found to be stable at 110°C., but at 170°C. the added mole of 8-hydroxyquinoline was lost completely. These observations have been substantially confirmed in the University of Illinois Laboratories (92). Ishimaru (125) also studied the procedure, and Berg recommended Hecht and Reich-Rohrwig's general method in his monograph (17).

Hecht and Ehrmann (113) recommended precipitation of thorium from acetic acid solution buffered with ammonium acetate for both micro and macro determinations and preferred the procedure to that employing picrolonic acid on the bases of rapidity and simplicity. An important application to the separation and determination of both cerium and thorium was made by Berg and Becker (18). Based upon the fact that the cerium(III) derivative could not be precipitated from solutions containing acetic acid, their method consisted in reducing cerium(IV) with hydroxylamine hydrochloride, adding sufficient acetic acid to give 2.5 per cent by volume in the final solution, and precipitating thorium from the boiling solution with excess oxine acetate solution, ammonium acetate being added as buffer if necessary. Precipitation of cerium was then effected from the filtrate by adding sodium tartrate and ammonia to raise the pH and treating at 60°C. with alcoholic oxine solution. The final determination was carried out in each instance by igniting the precipitate with oxalic acid and weighing the resultant oxide. Results accurate to less than 0.5 per cent were obtained for a variety of mixtures (18).

The best conditions for gravimetric estimation of thorium by this means involve final precipitation at 70°C. or above. As in all determinations involving 8-hydroxyquinoline, pH control is essential. According to Gotô (102), complete precipitation of thorium occurs in the pH range 4.4–12.5, with no precipitation taking place below pH 3.7. To insure complete precipitation, therefore, provision is often made for neutralization with ammonia or caustic soda (115) prior to filtration. In this form, estimation of thorium in the presence of the rare earth elements would be inaccurate because of precipitation of the latter at higher pH values (92, 169). Sufficient differences do exist between the pH values required for precipitation of thorium and the trivalent rare earth elements to permit determination of the former in mixtures (92, 169), but extremely accurate control of hydrogen-ion concentration is necessary. The method is generally suitable but should be investigated further.

(7) Miscellaneous acids: A number of other organic precipitants have been

recommended for thorium, but little attention has been given them. Both salicylic acid (94) and ammonium salicylate (76) have been suggested, but results with the former have not been encouraging (146, 194, 195). The ammonium salt is said to be useful for both thorium and zirconium determinations (174). Pratt and James (205) reported quantitative separation of thorium from the rare earth elements by precipitation with phenoxyacetic acid, but this has not been confirmed. Use of cupferron as a precipitant was suggested by Thornton (229, 230), who reported complete precipitation in solutions containing ammonium acetate and acetic acid but incomplete precipitation in the presence of even traces of sulfuric acid. Matveev (171) used cupferron for thorium determinations in buffered acetic acid solutions after removing iron as sulfide. Information on the effects of rare earth materials is not available, but Lundell and Knowles (168) believed the method to be of no quantitative importance. Precipitation as alizarin-3-sulfonate (15) appears to offer promise for microchemical determination of thorium in the presence of the rare earth elements, but it does not effect separation from scandium. Quinaldic acid is also a potential reagent for thorium, since it has been found to precipitate neither the rare earth elements nor zirconium from cold solutions (80). From hot solutions zirconium precipitates were obtained, but they differed from those obtained with thorium in being soluble in acetic acid.

Hecht and Donau (109) discuss a series of microquantitative methods using benzenesulfinic acid and its *p*-bromo and *p*-iodo derivatives as worked out by Feigl, Hecht, and Korkisch (81). The thorium salts, $Th(C_6H_5SO_2)_4$ or $Th(C_6H_4XSO_2)_4$ ($X = Br, I$), are precipitated from hot solutions by addition of up to fourfold excesses of the acids or their sodium salts. The precipitates are removed by filtration, washed, dried at 110–120°C., and weighed. Benzenesulfinic acid and *p*-bromobenzenesulfinic acid are recommended for 1–4 mg. of thorium and the iodo acid for less than 1 mg. These methods appear to be convenient, but they are limited in scope, and no information about interferences is available. The comparatively low thorium content of each precipitate may be cited as an advantage of the method.

4. Miscellaneous gravimetric procedures

Few other gravimetric procedures have shown any promise. This is typical of precipitation with selenic acid (154), hydrofluoric acid (224), or tannin (233), and of the various older procedures employing double carbonates, double sulfates, or double oxalates. Such methods are better suited to the rough separation of thorium from other materials and must be followed by more refined methods for its ultimate determination (134).

B. TITRIMETRIC ESTIMATION

Comparatively few titrimetric methods have been reported for the determination of thorium. Of those which have been investigated, all are either involved, highly indirect, or inaccurate. As a consequence, the more accurate, although more tedious, gravimetric methods are preferred. A recent comparative study by Banks and Diehl (10a) may be cited as a reëmphasis of the need for accurate and simple titrimetric procedures, especially procedures adaptable to the estimation of thorium in the presence of other elements.

1. Direct acidimetric estimation

In a recent publication, Tanteri (227) has reported the estimation of thorium by addition of excess sodium hydroxide solution and back titration of the excess with standard acid after removal of the precipitated hydrous oxide. Chief among objections to such a procedure is the complication introduced by the presence of any element which forms an insoluble hydrous oxide or hydroxide. It can be regarded as an unimportant procedure except perhaps for the routine assay of pure thorium compounds.

2. Estimation as iodate

Volumetric estimation of both cerium and thorium by dissolution of the precipitated iodates in acidified iodide solution and titration of the liberated iodine with standard thiosulfate solution was reported by Chernikhov and Uspenskaya (58), results obtained volumetrically agreeing with those obtained gravimetrically. Estimation of thorium in the presence of cerium was effected by reduction of the latter with peroxide prior to precipitation of the iodate. Reoxidation of the filtrate with bromate then permitted precipitation of cerium(IV).

While other information on the iodate procedure suggests its adaptation to volumetric estimation to be feasible, both Jüstel (134) and Banks and Diehl (10a) have indicated need for further work in checking the method. These opinions are in accord with results obtained in the University of Illinois Laboratories (92), where repeated applications of the volumetric method to both pure thorium salt solutions and monazite samples have yielded a thorium recovery of not more than 98 per cent on the average. The major difficulty lies in the apparent impossibility of freeing the precipitate from adsorbed oxidizing anions (IO_3^- and NO_3^-) without effecting partial decomposition or dissolution of the precipitate. Use of alcohol by Chernikhov and Uspenskaya is to be questioned, as is their report of the formation of $4Th(IO_3)_4 \cdot KIO_3 \cdot 18H_2O$ as the precipitate. It appears (92) that the precipitate is, instead, the normal iodate. Further work is necessary before the merits of the method can be evaluated critically, particularly work in the presence of other elements. The advantage of initial precipitation from strongly acidic solutions is of such importance as to warrant an exhaustive study of the method.

3. Estimation as ferrocyanide

Attempts to determine thorium by potentiometric titration with ferrocyanide have given discouraging results, and the method is of no importance. Early work by Atanasiu (5) indicated the composition of the precipitate to vary with amount of added alkali ferrocyanide, and the titration curves obtained were such that electrotitration of mixtures containing thorium, lanthanum, and cerium compounds was virtually impossible. The investigations of Shemyakin and

Volkova (217a) confirm such observations. These investigators reported an inflection corresponding to precipitation of the normal ferrocyanide from pure thorium salt solutions. However, when cerium or cerium and lanthanum were present, two inflections, one corresponding to precipitation of cerium and the other to precipitation of thorium and cerium or cerium and lanthanum, resulted. Quantitative estimation was impossible.

4. *Estimation as oxalate*

Use of permanganate titration in conjunction with oxalate precipitation was offered by Gooch and Kobayashi (101) as a volumetric means of determining thorium. Either titration of excess oxalic acid after removal of precipitated thorium oxalate, or titration after dissolution of the precipitate in acid was found to be effective, but accurate results could be obtained only if the initial precipitation were effected by slow addition of the thorium salt solution to excess oxalic acid solution. The reverse procedure yielded basic salts of indeterminate compositions. Eichelberger and Bibler (79) used the method to advantage in estimating the thorium content of blood and muscle tissue, but, although the method is inherently accurate, it is applicable only in the absence of elements which are precipitated by oxalic acid.

Atanasiu (6, 7, 8) has reported the determination of thorium and the rare earth elements by potentiometric titration, using sodium or ammonium oxalate solution. The results obtained were generally unsatisfactory, since only a single inflection was obtained with a mixture of thorium with lanthanum and cerium. Estimation in alcoholic solutions was also impossible.

5. *Estimation as molybdate*

Direct titration of thorium with ammonium molybdate solution with diphenylcarbazide as external indicator was suggested by Metzger and Zons (179). Quantitative results were obtained without interference from the rare earth elements when titration was carried out at room temperature in acetic acid solutions buffered with sodium acetate, but the authors found the rose color produced at the end point to persist for not more than 15 sec. and to be difficult of identification without experience. Standardization of the reagent against a pure thorium salt solution and use of indicator solution at least 2 weeks old were essential. Kaufmann (139) recommended the method on a comparative basis for its rapidity but questioned its accuracy. The latter opinion is shared by Banks and Diehl (10a).

Banks and Diehl (10a) proposed two modifications of the molybdate procedure. The first of these amounts to precipitation of thorium as the normal molybdate from 7 per cent acetic acid solution, diphenylcarbazide being used to indicate completion of the precipitation process, followed by dissolution of the washed precipitate in hydrochloric acid, reduction of the molybdate with amalgamated zinc, and titration with standard cerium(IV) sulfate with ferroin as indicator. In this form, the method gave fairly reliable results when applied to pure thorium salts (errors up to 0.23 per cent) and to thorium–uranium combinations (errors up to 0.63 per cent), but was less accurate for thorium–calcium mixtures (errors up to 5.06 per cent) and was inapplicable to thorium–rare earth combinations. A second modification amounts to potentiometric titration in 7 per cent acetic acid medium with standard ammonium molybdate solution at 50–55°C. with a 0.1 *N* calomel reference electrode and a molybdenum wire indicator electrode. In this form, the method yielded better results with thorium–calcium combinations (errors up to 0.26 per cent). Extension to other systems appears highly desirable.

6. Estimation as 8-hydroxyquinolate

The gravimetric 8-hydroxyquinoline procedure for thorium, like most procedures involving this reagent, may be rendered volumetric by titration of the well-washed precipitate, preferably $Th(C_9H_6ON)_4 \cdot C_9H_7ON$, with potassium bromide–potassium bromate solution after dissolution in hydrochloric acid (18, 115, 169). Since bromination requires four atoms of bromine to each quinolate residue, a rather favorable factor characterizes the titration. Indigo-carmine may be used as an indicator, the color change being from blue through green to yellow. As a more standard practice, however, potassium iodide is added and iodine equivalent to excess bromate is determined with standard thiosulfate. Bromate titration is apparently accurate, but all of the previously discussed difficulties inherent in the use of 8-hydroxyquinoline as a precipitant also characterize this method.

7. Estimation as picrolonate

Kiba (141) has described a potentiometric procedure for thorium based upon titration of thorium picrolonate with standard titanium(III) chloride solution at 90–95°C. in 4 *N* acid and in an atmosphere of carbon dioxide. Under such conditions, reduction of nitro groups in the picrolonate residues occurs. According to Kiba (141), the method is limited to not more than 10 mg. of thorium expressed as metal. This procedure is not regarded as accurate (10a) and is of no importance for estimation of the element.

C. RADIOMETRIC ESTIMATION

Methods dependent upon radioactivity measurements must of necessity assume that radioactive equilibrium has been established between thorium and its decay products. Furthermore, such methods are complicated by the presence of radioactive materials from other disintegration series, and even reasonably accurate results cannot be obtained unless ample correction for other activities is made. In a measure, this may be done through preliminary standardization of the counter or electroscope used.

Direct measurements of radiations have been used for estimation of the thorium contents of minerals. Joly (133a) applied the method in this form to the determination of as little as 10^{-5} g. of thorium per gram of rock. Borgström (29) applied the method to the evaluation of thorium to uranium ratios by powdering the mineral, coating a surface of known area with a known amount of the mineral suspended in chloroform, and comparing rates of electroscope discharge for various samples. Sasahara (213) has also determined thorium contents of ores by radiation comparison. High accuracy does not characterize such procedures.

Much more work has been done with the so-called emanation method (10, 53, 116, 123, 240). This method depends upon sweeping gaseous decay products (i.e., thoron) out of the solutions to be analyzed and determining their activities by passing the mixed gases through an ionization chamber. Cartledge (53) checked the method against the pyrophosphate procedure of Carney and Campbell (52) and reported a maximum error of only 1.5 per cent. Helmick (116) refined the experimental technique but listed as disadvantages of the procedure the costly apparatus required, the necessity for freedom from vibration in the electroscope arrangement, and the necessity for complete absence of all other radioactive materials in the vicinity of the apparatus. To this might be added the absolute necessity for existence of radioactive equilibrium. Further improvements in the method have been made by Holmes and Paneth (123) and by Urry (240).

Because of the generally unsatisfactory character of the emanation method, Evans and coworkers (80a) proposed the following alternative procedures: (*1*) using a vacuum-tube electrometer to count all alpha particles emitted from smooth polished sample surfaces, (*2*) counting all alpha particles emitted from powdered specimens, (*3*) counting only the ThC′ alpha particles after excluding shorter-range alphas by use of suitable absorbers, and (*4*) detecting gamma rays emitted from larger sources with a sensitive screen-cathode counter. Of these alternatives, Evans considered methods 2 and 4 to be the most suitable. Method 3 gives the thorium content directly, while with the other methods correction for uranium content is necessary. With methods 2, 3, and 4, internal standardization may be employed. Use of alpha-particle measurements was employed by Finney and Evans (83a) for analyses of uranium–thorium mixtures, and gamma-ray counting was employed by Evans and Mugele (80b) for the estimation of thorium in rocks.

Radiometric titration using a standard disodium phosphate solution containing radiophosphorus has been suggested by Langer (160a) for the estimation of a number of elements, among them thorium. Although successful application of the method to thorium was hampered by the colloidal character of the thorium precipitate, the procedure appears entirely feasible. In principle it is dependent upon establishment of the equivalence point through a steady decrease in activity of the solution until precipitation is complete, followed by an increase as excess of the reagent is added.

D. ESTIMATION BY MISCELLANEOUS PROCEDURES

The successful polarographic estimation of thorium has been reported by Kryukova (159). Except for spectrographic or spectrometric methods, no other specialized procedures have been employed (134).

Spectral methods for thorium analysis have been employed for many years

(78, 85, 89, 224), but the quantitative aspects of these methods have received attention only in recent years. Thus, Parson (201) determined the thorium contents of thoriated tungsten filaments with mean deviation of ±3.54 per cent and maximum deviation of ±5.3 per cent by use of the 2899.3 Å. line as excited in a 2200-volt A.C. arc and of chemically analyzed comparison standards.

X-ray spectrographic methods have been explored more thoroughly (88, 89). Borovskiĭ and his coworkers (30, 31) reported determinations of thorium in error by some 5–20 per cent by this means, although by a refined technique errors were reduced to 5–7 per cent for synthetic thorium–rare earth mixtures. Improvements in analytical technique have been described by Komoviskiĭ and Golovchiner (149, 150), and Voronova (242) has obtained excellent results in the x-ray analysis of minerals with both high (35–50 per cent) and low (0.1 per cent) thorium and uranium contents, using strontium as a comparison element.

E. SUMMARY

Consideration of the quantitative methods listed indicates that most accurate results are still obtained by gravimetric means. If separation of interfering elements is complete, precipitation of thorium with ammonia or oxalic acid and ignition to the weighable oxide is a standard procedure which will invariably give reliable results. Oxalate precipitation has the further advantage of being directly applicable to thorium materials containing uranium, zirconium, hafnium, and titanium. In the presence of the rare earth elements, separation as iodate appears to be the most feasible preliminary to oxalate precipitation from the points of view of accuracy, cleanliness of separation, and time requirement. Other proposed means of separation appear to offer no major advantages, although further investigations upon certain of the organic precipitants such as hexamethylenetetramine, 8-hydroxyquinoline, *m*-nitrobenzoic acid, and sebacic acid are indicated.

No titrimetric procedure yet developed can compare in accuracy with the gravimetric methods. However, for routine assay where extreme accuracy is not essential titrimetric methods offer advantages in convenience and in rapidity of use. Of the methods proposed, those involving iodate and molybdate appear most promising and merit further considerations. Radiometric and other miscellaneous procedures are adaptable, at least in their present forms, only to analyses under specialized conditions, and their extension to routine and highly accurate work is extremely unlikely.

V. ANALYSIS OF THORIUM-CONTAINING MATERIALS

Applications of methods already outlined to the analysis of thorium-containing materials are considered in detail in the standard reference works (24, 26, 38, 89, 120, 163, 185, 215, 224, 234). Among such materials, those usually encountered are thorium compounds, minerals, alloys, catalysts, and incandescent-mantle residues (90). In all instances, analysis may be effected by procedures previously recommended, but ultimate analysis must, except when applied to relatively pure thorium compounds, be prefaced by sample preparation and removal of interfering elements. Methods suited to such separations have already been treated in detail.

Thorium-bearing minerals may be divided roughly into those rich in thorium (*ca.* 50–60 per cent ThO_2) and those poor in the element (*ca.* 4–10 per cent ThO_2). Representative of the first group are the silicate thorite and the oxide thorianite, and representative of the second class are the phosphate minerals monazite and xenotime and certain rare titano- and tantalo-columbates such as euxenite, fergusonite, and samarskite. Minerals rich in thorium are usually decomposed with hydrochloric or sulfuric acid, silica being removed by dehydration and the heavy metals by saturation with hydrogen sulfide (215, 224). Thorium (and any rare earth elements or yttrium present) is then precipitated with oxalic acid and analysis continued in the usual fashion.

Of the minerals which are poor in thorium, only monazite or monazite sand can be regarded as an important source of the element. Most of the thorium which is recovered technically does, however, come from this source, and the problems associated with its removal from the comparatively large quantities of rare earth elements which accompany it are still considerable. For analysis, a weighed quantity of the sand is usually decomposed by heating with excess concentrated sulfuric acid for several hours, after which the thick mass is added slowly to ice water and stirred until the sulfates have dissolved (120, 124, 215). After filtration, the thorium may be roughly separated from the rare earth elements by careful reduction of acidity through dilution or addition of magnesium oxide (224) and subsequently estimated after phosphate removal, or the solution may be diluted to a given volume and an aliquot analyzed by some method applicable to strongly acidic media (120). If the thorium content is exceptionally low, fusion with sodium fluoride and potassium pyrosulfate followed by leaching with hydrochloric acid and precipitation with oxalic acid is sometimes preferred as an alternative procedure (120).

Thorium-containing alloys are usually decomposed with either hydrochloric acid or sulfuric acid (134), although thoriated tungsten wires are better treated by direct chlorination or by dissolution in mixtures of hydrofluoric and concentrated nitric acids (134). Acid treatment is also applicable to catalysts, since cobalt, nickel, iron, magnesium, and silica are the materials most commonly present (134). Subsequent analysis of these acid extracts is effected in all instances by the usual methods.

Residues from the mantle-lamp industry consist primarily of thorium materials, together with comparatively small quantities of cerium compounds. Since these residues usually amount to oxides prepared by high-temperature reactions, they are perhaps best solubilized by acid fusion, say with alkali bi- or pyro-sulfate. Removal of cerium is desirable before estimation of thorium is attempted.

VI. CONCLUSION

In analytical characteristics, thorium bears an exceedingly close resemblance to scandium, yttrium, and the rare earth elements, particularly to cerium(IV) and to the least basic members of the yttrium subgroup. The analytical chemistry of the element is, therefore, complicated by the necessity for removing these interfering elements. Thus far, most of the reported processes for effecting such separations are either fractional in character or tedious and costly of operation. As a consequence, the development of clean-cut analytical methods for thorium has been slow, and present-day procedures are largely inadequate. It is to be hoped that renewed interest in the chemistry of the element will result in the development of rapid and accurate methods for its detection and estimation and that the problems imposed by the presence of the rare earth elements will meet with ultimate solution. Certainly, the need for further investigation is apparent from the summary here presented.

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PROPERTIES OF ALKYLBENZENES[1]

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This paper includes a tabular compilation of the physical properties of all alkylbenzenes described in the literature through 1947, so far as found by the author, together with a critical review of the evidence for identity in several doubtful cases. Tentative identification is suggested for some new hydrocarbons.

Approximate functions of structure in simple form have been found for the properties as follows:

$$d_4^{20} = 0.850 + (0.12/n)(1 + a + b)$$

$$d_4^{20} - 0.854 = 27(n_D^{20} - 1.475)^2$$

$$\text{B.p.} = 18n + 21 - 1800/n^2 \quad \text{(for } n\text{-alkylbenzenes)}$$

(similar equations for boiling points of other alkylbenzenes)

$$\text{M.p.} = 19n - 0.3n^2 - 247$$

(for normal and three other classes of alkylbenzenes)

The letter n in the equations is the number of carbon atoms; a is the number of pairs of adjacent alkyl groups; b is 1 for mono-*tert*-alkylbenzenes, and 0 for all other aromatics.

These relations have been used to calculate the properties of most of the alkyl benzenes listed. The calculations of properties not observed are included in the table; and observations differing substantially from the calculations are questioned. Correlations with the observations are shown graphically and discussed.

I. INTRODUCTION

Monocyclic aromatics with saturated side chains, or alkylbenzenes, constitute one of the most important classes of hydrocarbons. This is also one of the largest classes, the number of known members exceeding the known paraffins by over one hundred. This review contains a concise list of 379 alkylbenzenes, with observed properties which are recorded in the literature. It also includes a critical discussion of the evidence for structure in about eighty doubtful cases and, in addition, simple but comprehensive correlations of the properties of all members of this class of hydrocarbons.

Two general compilations of such physical properties have been made in addition to Beilstein (30) (which lists only 175 alkylbenzenes in all three volumes) and others with less than 100 alkylbenzenes (7, 8, 231, 353, 382). Doss (87) selected a single observation for each value, but since the latest edition is four years old, it omits 117 alkylbenzenes which can now be included. Egloff's compilation (95) is more recent and lists several observations on each property when available, but many of the best observations were restricted during the war and so could not be published. About 112 alkylbenzenes now described in the literature are not included in that list. Moreover, for 58 other alkylbenzenes which are listed in Egloff's compilation, observed values for one or more additional properties are now available.

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[1] The portion of this paper which deals with the calculation of physical properties, together with the graphs, was presented before the Division of Petroleum Chemistry at the 112th Meeting of the American Chemical Society, New York City, September, 1947.

Many of the published observations, sometimes the only one on a certain hydrocarbon, are "casual observations", that is, made on impure material, or material of uncertain structure, or, in the case of boiling points, without stem correction or barometer reading. This does not mean careless work, since the investigator was not determining physical properties, and the hydrocarbon may have been an incidental by-product in which he had little interest. For many alkylbenzenes an assumption of an average value of 0.86 for density and 1.49 for refractive index would be less in error than to use the published observations. For example, the *lowest* of the fifteen observations on the density of isobutylbenzene included in Egloff's compilation (95) is 0.8628, although the value now accepted (8) and supported by three recent excellent observations (50, 121, 142) is only 0.8532. Similarly, the *highest* of fifteen previously recorded normal boiling-point observations for it is 171.0°C., compared with the now accepted 172.8°C. (8) (supported by 38b, 50, 121, 328). The explanation may be that most of the older observations were actually made on *tert*-butylbenzene, since they agree fairly well with good values for the latter. Schramm (308) in 1888 was clear on this point, and reported good observations for the density and boiling point of both hydrocarbons. The evidence for structure in some of the other early papers is lacking or inadequate. Even recently, observations on the densities of three alkylbenzenes not higher than C_{13} in the *Journal of the American Chemical Society* seem to be about 9 per cent too high, judging by other observations on the same or related hydrocarbons.

Nevertheless, observations on so large a number of alkylbenzenes are available that relations are discernible, if some erratic observations are disregarded.

In order to judge the reliability of an observation or to choose between badly discrepant ones, it is desirable to have a comprehensive correlation between the properties and structures of hydrocarbons. Three papers by Corbin, Alexander, and Egloff (70, 71, 72) have already correlated the properties of the simpler types of alkylbenzenes,—namely, the 1- and 2-phenylalkanes,—and some of the dialkylbenzenes, but less than one-seventh of the total number of known alkylbenzenes are included. In a fourth paper (73) the same authors showed the relation of boiling point to pressure for some additional alkylbenzenes. Other more general but less accurate correlations for boiling point are those of Kinney (184) and Klages (200). Curves correlating the properties for certain series of alkylbenzenes were drawn by Schmidt and coworkers (302, 304, 305). Ward and Kurtz (382) have shown relationships between boiling point and other properties for the lower alkylbenzenes.

Since the more complex hydrocarbons are the less common and therefore the more in need of tests of reliability, it was felt that the correlation must be applicable to every member. It should also be as simple as possible, even though empirical. This was the attitude in the analogous correlation of all paraffin hydrocarbons (106, 107) and seems to have been justified by the results. For example, the average deviation of the calculations from the values selected by the Bureau of Standards (6) two years later for the 35 nonanes, eleven of which were unknown at the time of the calculations, were for the boiling point 0.92°C., for density 0.0013, and for refractive index 0.0008. Later the Bureau of Standards made calculations (358) by an independent method for all three properties, but applied it only up to the nonanes. Recently Wiener (391) developed still another method by which he calculated boiling points for paraffins up to decanes. The three methods give comparable precision except for paraffins containing two quaternary carbon atoms. The earlier method (106) seems better adapted for this type, but this also gives low values for some paraffins with five or more branches (149a). The calculations have facilitated other researches (for example, 149, 173). The former (and also citation 352, p. 68) confirmed an error of 7°C. in the observed boiling point of one nonane, which had been pointed out in the calculations (106). The present calculations for alkylbenzenes are probably less accurate than those for the paraffins, because the data on which they are based are on the average much older.

II. DESCRIPTION OF TABLE

Table 1 (see Section VIII) lists every alkylbenzene found by the author in the literature for which one or more of its observed physical properties is given. The names of some alkylbenzenes listed in Doss's (87) and Egloff's compilations are reworded or renumbered for consistency with the Bureau of Standards table (8) and usage in *Chemical Abstracts*. However, when used in the name, a phenyl group is listed first and given the smallest possible number, because it is considered the most important radical. Sometimes an alternative name is added in parentheses, which is shorter and acceptable, though less formal. A precise arrangement is used in the table to permit easy location of a hydrocarbon, or a conclusion that it is unknown. The arrangement is substantially the same as that of Beilstein (30) and of Egloff (95). Isomers are listed in order of increasing number of substituents, and of the positions of substituents in the order phenyl, methyl, ethyl, etc., and normal, secondary, iso, and tertiary. "*Sec-*" is used only for butyl groups (except in a few cases of uncertain structure), and "*tert-*" is used only for butyl and amyl groups. For these there is no ambiguity. The table includes the 18 unknown C_{11} alkylbenzenes with properties calculated by methods of this review, and also a C_{12} alkylbenzene, described in the literature, but later shown to have a structure different from that assigned. These 19 unknown hydrocarbons and benzene are not counted in the "379 alkylbenzenes" mentioned above.

Observations of the boiling point at pressures of 710–775 mm. were corrected to 760 mm. by the relation applicable to alkylbenzenes (correlated from the values of references 7 and 8):

$$dt/dp = 0.035 + 0.0001t$$

No attempt was made to convert boiling points at low pressures, although this conversion is facilitated by a recent paper (73), because the pressures given are not usually sufficiently accurate. In view of the high thermal stability of aromatic hydrocarbons, it is unfortunate that normal boiling points were not observed in many more cases. For about 57 alkylbenzenes boiling below 300°C. the only reported boiling points are those at low pressures, which are of little value in identification.

Observations of density and refractive index at temperatures different from 20°C. were corrected to that temperature by the relations of Lipkin and Kurtz (224). Approximately the coefficients are $dd_4^{20}/dt = -0.00075$, and $dn_D^{20}/dt = -0.00045$.

The numbers of theoretically possible isomers in the first column were taken from a recent paper (109).

The properties listed for C_6 to C_{10} hydrocarbons are substantially those chosen by the A. P. I. Hydrocarbon Research Project No. 44 (7, 8), with trifling revisions for more recent publications. Only a few supporting citations are given for each hydrocarbon, since the hundreds of references available would add little in reliability to those given. For example, eighty-three citations have been found prior to 1875 for "cymene", presumably *p*-cymene, many of which agree well with the now accepted values. Wright (393) reviewed some of them, and gave boiling points of material from eight different sources. Gladstone (127) reported good values for density and refractive index for the same samples. There is a still larger number of early references on benzene, toluene, and the xylenes which are of historical interest only.

The properties listed for the alkylbenzenes containing more than ten carbon atoms are selected means when more than one observation is available for any value. The selection was made on the basis of preponderance of agreement of observations, except that in the case of melting and boiling points the higher values are given increased weight because impurities are more likely to cause low results. An error on the low side would result also from neglect of stem correction. Galle's method (117) of correcting boiling points is theoretically sound if not extremely accurate. His corrected value for hexaethylbenzene, 305°C., is higher than those of fourteen other observers, although only 1.6°C. above that of the present author (110).

In making the choices all of the observations cited by Doss (87) and by Egloff (95) were considered and checked, about 90 per cent of them by the use of the original literature, and most of the remainder by the use of abstracts. The book by Thomas (358a) and the chapter by Price (284a) proved fruitful sources of references. Over one thousand additional observations (on alkylbenzenes above C_{10}), including many too recent for those books, were found and considered. These were the source of the data on the additional hydrocarbons. Since Egloff's compilation presents hundreds of citations on the properties, it seems unnecessary to repeat them all here. However, the present bibliography is intended to be complete for observations on the properties of alkylbenzenes above C_{10} which are *not* included in Egloff's book. Two C_{10} hydrocarbons, *o*- and *m*-*n*-propyltoluenes, also are covered completely in this respect, since the lack of melting-point values, or of decimal points on the boiling-point selections by the Bureau of Standards (8), probably indicates that they have not, like their isomers, been given recent accurate study. Several of Egloff's citations are repeated in order to cover the most reliable observations on each property, and also some observations not mentioned by him, although included in the citations. Page numbers show the exact location of data except in about twenty-five foreign citations which were not available (indicated by a plus sign after the page number). The abstract reference or other actual source of the data is appended for these and some other citations. Preference is given to *Chemical Abstracts*, or for the earlier papers to *British Chemical Abstracts*, unless some observation is omitted there and included in *Chemisches Zentralblatt* or other source listed. The listing of two secondary sources usually means that each contains pertinent data which are omitted from the other. The spelling of authors' names follows that of *Chemical Abstracts* (or the *British Chemical Abstracts* cumulative index), even in preference to the original spelling in foreign journals.

Question marks are applied in the table to observations far out of line with those of hydrocarbons of similar structure (more than 5°C. in boiling point or melting point, or 0.01 in density, or 0.006 in refractive index, according to the correlations of this paper), and not well established experimentally; and suggested revisions calculated below are included, enclosed in parentheses. The same notation is used also for several values for which no observation has been made. A question mark after the numerals in the name of a hydrocarbon indicates uncertainty in the positions of the groups; and one after the name shows doubt of the whole structure. A question mark after a reference number indicates similar doubt of structure in that reference.

III. DISCUSSION OF IDENTITY

Doubts of the identity of some of the hydrocarbons named in the literature have appeared in the light of other citations, or from the physical properties, or by experience in the reactions. Some of these considerations are as follows: It is generally agreed that in the Fittig and Grignard reactions the alkyl groups remain unchanged and replace the halogens of the ring. In the Friedel–Crafts reaction the resulting alkyl groups above ethyl are rarely primary except from cycloparaffins (132, 166, 324) and primary alcohols (166), and under mild conditions from primary esters or halides (166), especially those with long chains (125a, 312). They are usually secondary from straight-chain olefins and other reagents, and tertiary from reactants having a branch adjacent to the double bond or other functional group. The phenyl group frequently assumes a position different from that occupied by the functional group of the reagent (156, 371); but in the case of secondary alcohols (156) the position can be predicted with good probability by postulating a preliminary decomposition of the alcohol to olefin, followed by addition of the aromatic to one side of the double bond according to Markovnikov's rule.

The positions assumed by the alkyl groups are seldom ortho or vicinal (1,2,3- or 1,2,3,4-) in appreciable amount if it is possible for them to be further apart. The possibility of migration of alkyl groups should be considered. When two or more products are possible and two are found, the higher-melting one is probably the more symmetrical; and the one with higher boiling point, density, or refractive index is probably the one with more pairs of adjacent alkyl groups, especially if one of the groups is methyl. Gilman and Meals (124) have discussed the evidence of identity in many cases.

Each statement in the following discussion is intended to correct an apparently inaccurate designation (indicated usually by quotation marks) of some alkylbenzene in a compendium or literature article, or to facilitate identification of a hydrocarbon whose structure was incompletely established. On the other hand, the structures assigned tentatively to some of the hydrocarbons not previously listed are admittedly rather speculative.

The possible mistaking of *tert*-butylbenzene for isobutylbenzene has been mentioned already. There is similar confusion in some of the early literature between amyl derivatives, especially normal, iso, and tertiary. The "*o*- and *m*-cymenes" of Claus and coworkers (67) probably contained *n*-propyl groups, in view of their synthesis from propyl bromide by the Fittig reaction and the high boiling point of the ortho isomer, although that of the meta isomer is low.

The dimethylethylbenzene of Anschütz and Romig (9a) must have been symmetrical rather than "1-ethyl-2,4-dimethylbenzene" (95), because it gave uvitic acid on oxidation. O'Connor and Sowa (263) made 2-phenylpentane instead of "1-phenyl-2-methylbutane" (95).

The methylbutylbenzenes of Kozak and Novak (207) had *tert*-butyl groups (as they showed) instead of normal ones (95). Similarly, Baur (25) showed that the product which Kelbe and he (180) had called "1-methyl-3-isobutylbenzene" contained a tertiary group. Since Effront (94) considered his product the same, it too can be regarded as 1-methyl-3-*tert*-butylbenzene. Apparently no isobutyltoluene has ever been made and described. The hydrocarbons called "1-methyl-4-isobutylbenzene" (87, 95) were both 1-methyl-4-*sec*-butylbenzene (237, 379). Brun (48a) gave no properties or identification for his "isobutyltoluene." Kelbe and Baur's "*p*-butyltoluene" with a "butyl group of unknown structure", boiled at 176–178°C. Since the only evidence for $C_{11}H_{16}$ composition was elementary analysis (the difference being slight), the low boiling point makes the substance look like *p*-cymene, as suggested by Tafel (355) and by Noelting (257). For "metaethylpropylbenzene" (288) there is no evidence for the structure assigned to the alkyl groups. Since the propyl groups in Renard's other products were iso, this one too was probably secondary. It might even be 1-methyl-3-*sec*-butylbenzene, but in either case the assigned structure would be unknown.

The evidence of Claus and Eller (66) for the structure of their "isoamylbenzene" is good except for the elementary analysis, which is far too low in hydrogen, as noted by Bygden (56). On the other hand, the isoamylbenzenes of Menshutkin (236) and Stratford (350) probably had that structure rather than "2-phenylpentane" (95). The "trimethylethylbenzene" described by Glattfeld and Milligan (130) was not "1-phenyl-2,2-dimethylpropane" (95) but 2-phenyl-3-methylbutane.

Tilicheev (359) made it clear that almost all of the alkylbenzenes described by him (360) and by him and Kuruindin (361) were secondary (2-phenylalkanes); but most of them have been listed in one or more compilations (95, 302, 304) as "normal alkylbenzenes" and even the abstracts are not definite. Brochet (47) and Khardin (181) identified their hexylbenzenes as 2-phenylhexane and 1-phenyl-3-methylpentane, respectively, rather than the normal compounds (95). Kruber's heptylbenzene (212) probably was secondary; and Ciamician assigned no structure to his $C_{13}H_{20}$ product (63). The "ethylhexylbenzene" of Hennion and Toussaint (144) probably had the tertiary structure, 3-phenyl-3-methylheptane.

Tafel (355) found that the monoalkylbenzenes to which he and his coworkers (356, 357) had assigned the structures "1-phenyl-2-methylbutane" and "2-methyl-2-benzylbutane" were probably *n*-amylbenzene and 1-phenyl-3-methylpentane, respectively. The properties and syntheses are more consistent with the latter structures. The second hydrocarbon mentioned must be considered unknown.

The "β-methyl-δ-phenylpentane" of Berman and Lowy (33) may have been a mixture with 3-phenyl-2-methylpentane (*cf.* 156). Huston and Kaye (156) made twenty products, not all of which were identified by name, but it was made clear that some of the others were binary or ternary mixtures of isomers. The probable components include a branched hexyl and five branched heptylbenzenes which are otherwise unknown. These are listed in the present table with appropriate brackets. (One hydrocarbon is slightly out of order to permit bracketing.)

Essner and Gossin's identification (98) of their principal product as *m-tert*-amyltoluene (supported by references 62, 257) seems justified rather than "1-methyl-3-*n*-pentylbenzene" (95). They did not identify their lower-boiling product, which from its synthesis might be 1-methyl-3-(1′,2′-dimethylpropylbenzene (*cf.* 206 for the corresponding amylbenzene). Similarly, the *p*-amyltoluene of Kunckel and Ulex (213) and one of the amyltoluenes of Tsukervanik (371) seem to contain the 1′,2′-dimethylpropyl group, assuming the mechanism implied in the papers. The branched "amyltoluene" of Avenarius and Link (17a) was considered by Noelting (257) to be a butyltoluene.

Although Uhlhorn (374) gave evidence for the ortho structure in his diisopropylbenzene, Heise and Töhl (141) claimed that it was para. This would make the ortho isomer unknown until 1947 (235b), although it is listed in several compilations (70, 87, 95, 353). The new low boiling point supports the view of Heise and Töhl. Genvresse (119) and McKenna and Sowa (230) both indicated a para structure for their diisopropylbenzenes rather than meta (95) or ortho (87), respectively.

Nightingale, Radford, and Shanholtzer (253) and also Buu-Hoi and Cagnaint (54) showed that the "1,3-dimethyl-4-*tert*-butylbenzene" of Nightingale and Smith (255) was largely the 1,3,5-isomer. On the other hand both groups of authors confirmed the identity of the former structure for the product made by Smith and Perry (340). The latter investigators' observations of density and refractive index are incredibly high, and no values for these properties were given by Buu-Hoi and Cagnaint (54).

The hydrocarbon of Böeseken and Wildschut (42) was not "*n*-heptylbenzene"

(95), since it was made from 3-ethylpentane. It probably had the otherwise unknown structure, 1-phenyl-3-ethylpentane.

Kirrman and Graves (185) did not identify their diisopropyltoluene. Although they reported largely hemimellitic acid on oxidation of the fraction containing it, the vicinal structure is very improbable considering its synthesis, the low values for density and refractive index, and the analogy in color reaction to that of their 1,2,4-triisopropylbenzene. The structure 1-methyl-2,4-diisopropylbenzene seems most probable.

The only observation on the density of 1-methyl-3-ethyl-6-*n*-butylbenzene—0.6882 at 11°C. (232)—is an obvious typographical error, which is copied in Beilstein (30c) and in three abstracts, though questioned in *Chemisches Zentralblatt.* Doss (87) took the value 0.8882, but the slightly lower value, 0.8862, selected by Egloff (95) seems more probable. The density (0.8550) given by Larsen, Thorpe, and Armfield (217) for hexadecylbenzene was inadvertently assigned to hexaethylbenzene (95); and that assigned to di-*tert*-butylbenzene (95) should apply to the mono derivative (153). The melting points assigned (95) to the 1,2,4- and 1,3,5-triethylbenzenes (333) and to triisopropylbenzene (248) should apply to derivatives.

Barbier (19, 20, 21, 22) made by alkylation six of the ten theoretically possible methylisopropyl-*tert*-butylbenzenes, but assigned structures to only three of them, the 1,4,2- and 1,4,3- (22) and 1,3,5-isomers (21). The others can be identified with fair probability as follows: Three other possible structures (1,2,3-; 1,2,6-; and 1,3,2-) are vicinal trialkylbenzenes, and are very unlikely to result from alkylation. Eliminating these as probabilities, one of the other products, the one boiling at 235°C. under 737 mm. (Barbier's "2") (20, 21), must be the 1,2,5-isomer, since it was made from *m*-*tert*-butyltoluene and the other possibilities are accounted for. The product boiling at 236°C. under 727 mm. (Barbier's "3") must be the 1,3,6-isomer, since it was made from *p*-*tert*-butylcumene (22). The remaining product (Barbier's "1"), which boiled at 230°C. under 733 mm., was made from *p*-*tert*-butyltoluene and could have its isopropyl group in either the 2- or the 3-position. Steric influences favor the former, but the relatively low boiling point favors the isomer with no alkyl group adjacent to the methyl group (1,3,4-).

Timmermans listed a tetraethylbenzene as "1,2,3,4?". The numbering probably should be "1,2,4,5-" because of the high melting point, 11.6°C. (*cf.* 171, 334), since the former freezes below −50°C. (334), also < −20°C. (117, 170). The vicinal structure is copied without a question mark in *Chemical Abstracts* and in compilations (95, 353). Galle (117) considered his tetraethylbenzene to be the 1,2,3,5-isomer, because on oxidation it gave prehnitic acid. The literature on the structure of the latter is equivocal; and Jacobsen (170) showed that Galle had the vicinal derivative. This was confirmed by Smith and Guss (355), who formed only the 1,2,3,4-isomer by the Jacobsen reaction used by Galle (117).

Denisenko (81) used an ingenious method, the catalytic reduction of phenyl-ω-cyclopentylalkanes, to make mixtures of monoalkylbenzenes. Each product contained presumably the *n*-alkylbenzene and (except for C_{11}) two other 1-phenylalkanes in which the alkyl group had one methyl or one ethyl group side chain, respectively. The products above C_{11} were incompletely separated. The higher-boiling cuts from the C_{15} and C_{16} products are assigned structures of the normal alkylbenzenes, and the lower-boiling cuts are considered to be mixtures of the other two predicted isomers, which should have almost identical properties. The high densities and refractive indices of the products may indicate incomplete rupture of the cyclopentyl ring.

Similarly Fleischer and Melber (102a) obtained a C_{14} alkylbenzene by Clemmensen reduction of a bicyclic diketone and indicated four possible structures, depending on the point of rupture of the second ring. Reaction probabilities and the high values of the observed density and index both favor the two structures with three alkyl groups, of which one is selected tentatively,—namely, 1,2-dimethyl-3-(2′-ethylbutyl)benzene.

The structure of the "methyloctylbenzene" described by Joukovsky (174) is not given. From its synthesis the most probable structure is 1-methyl-4-(1′,5′-dimethylhexyl)benzene (made also by Ruzicka and van Veen (295)), but since Joukovsky showed it to contain double bonds in substantial amount, it must be impure.

The unsymmetrical structure, 1,3,4-, was assigned by de Capeller (59) for his di-*tert*-butyltoluene because the same product resulted on dialkylation by means of aluminum chloride, which according to Baur (25) gives *m*-*tert*-butyltoluene, or on dialkylation by means of ferric chloride, which Bialobrzeski (37) found to give *p*-*tert*-butyltoluene. The latter observations were supported by Noelting (257), by Buu-Hoi and Cagnaint (52), and partly by Pajeau (265a), but not by Shoesmith and McGechen (318). However, this evidence for the structure of the di-*tert*-butyltoluene is not very convincing, in view of the reluctance of branched-chain alkyl groups to assume adjacent positions, of the weakness of directive influence in alkylation (110, 284), and of the facility of rearrangement (213, 306), especially in the nascent state. Noelting (257) proved that his di-*tert*-butyltoluene, similarly made, was symmetrical because it formed a trinitro derivative. The comparatively high melting point, 32°C. (59), also favors the symmetrical structure.

For similar reasons a symmetrical structure is assigned in this compilation, and also in Nightingale's review (250a), to the tri-*tert*-butylbenzene which melts at 128°C. Senkowsky (313) did not indicate the positions; and R. A. Smith (341) gave no evidence for the positions "1,4,6-" by which he designated it (*cf.* 95), although the presumed intermediate, *p*-di-*tert*-butylbenzene, suggests the unsymmetrical arrangement (*cf.* 306 for analogous rearrangement of isopropyl groups). The liquid "tributylbenzene" described by Ipatieff and coworkers (160, 162), which may be the same as that of Koch and Steinbrink (202) and of Kunckel and Ulex (213), is assigned tentatively the 1,2,4- structure, although Legge (218a) has evidence for more complex reactions upon the per-alkylation of benzene with isobutene. Firla's "tributylbenzene" (102) had a boiling point too low for any tributyl- and too high for a dibutyl-benzene. His products may be similar to those of Legge. The properties of some of Legge's fractions (218a) are listed in table 1 after the structures assigned, even though separation was incomplete, because calculated properties for structures comprising a fraction are nearly alike.

The structure 1,3-dimethyltetraethylbenzene is assigned in table 1 to the product of Staudinger and coworkers (345) since they employed "pure xylene", which was probably m-xylene. Galle's product (117) was probably the same.

The positions of most of the alkyl groups are not given in the polyalkylbenzenes of Dreisbach (89, 90) and Dreisbach and Heusted (91). The products were probably mixtures, but the structures assigned are preferred for the reasons given. For the ethyldiisopropylbenzene the symmetrical structure is most common in alkylation under vigorous conditions. Similarly, the 2,4,6-positions are assigned tentatively to the three isopropyl groups in derivatives of toluene, ethylbenzene, xylene, and diethylbenzene. No structure is assigned to the diethyldiisopropylbenzenes. The ethyl groups are probably meta. One of the ethyltriisopropylbenzenes probably has the structure 1,2,4,5- and the other 1,2,4,6-. The product with the high melting point, 106.9°C., is assigned the more symmetrical structure, 1,2,4,5-, by analogy with durene and the corresponding tetraethyl- and tetraisopropyl-benzenes, all of which have high melting points.

The two triethyldiisopropylbenzenes were both made from "triethylbenzene". Since the symmetrical isomer could give only one diisopropyl derivative, the other product must result from unsymmetrical triethylbenzene (the vicinal isomer being unknown). The lower boiling point is assigned to the product from the symmetrical isomer, because it lacks adjacent ethyl groups. In the tetraisopropyltoluene the positions of the four isopropyl groups are practically determined by analogy with the only known tetraisopropylbenzene (symmetrical).

Tilicheev's *m*-diamylbenzene (360) probably had *sec*-amyl groups, and the Sharples product (316) might be the same, or it might contain tertiary groups; but the amylbenzenes of Austin (10) and Costa (75) were probably *m*-di-*tert*-amylbenzene, because they were made from optically active amyl alcohol.

The two "triamylbenzenes" of Ipatieff, Corson, and Pines (160) showed very different boiling points, and had perhaps secondary and tertiary radicals, respectively. The Sharples product (316) may be the same as the higher-boiling one (*sec*-), although there are 920 possible triamylbenzenes (*cf.* 109). The dioctyl- and dinonyl-benzenes (160) and Tilicheev's diheptylbenzene (360) probably had secondary groups.

The hydrocarbon of Schaeffer and Stirton (297a) is assigned the structure 9-phenyloctadecane, since it would result from either 9- or 10-phenyloctadecanol in their mixture.

Two hydrocarbons, bombicestane, $C_{27}H_{48}$, and inagostane, $C_{29}H_{52}$, listed by Egloff (95) are omitted from this compilation, since they probably are not alkylbenzenes but tetracyclics, because of their close similarity to cholestane (178a, b).

The following hydrocarbons listed in a compilation or abstract must be considered unknown, since the names apply to alkylbenzenes described apparently correctly by the original authors under different names: "1,2-di-*n*-propylbenzene"

(95, 137); "3-methyl-4-phenylhexane" (4); "2-*p*-tolylhexane" (95, 344); "1-propyl-2-*n*-pentylbenzene" (43, 95); "1,3,5-trimethyl-2-(2′-methylbutyl)benzene" (95, 199); "1-methyl-3,5-di-*n*-butylbenzene" (95, 257); "3-propyl-3-phenylheptane" (95, 138); "1-methyl-5-undecylbenzene" (87, 140); "1,4-di-*sec*-hexylbenzene" (95, 344); "2,8-dimethyl-3-propylnonane" (95, 138); "5-phenyl-2,8-dimethyl-8-isobutylnonane" (87, 138). This would apply also to "2-phenyl-3-methylhexane" (87, 138), except that it was probably present in one of the products of Huston and Kaye (156). Some of these names are doubtless typographical errors.

Typographical errors in the original literature include observations on density: 0.0834 (380), 0.959 (124), 8.0638 (174), and observations on refractive index: 4.92 (185), 2.522 (247). These values probably should be 0.8834, 0.859, 0.8638, 1.492, and 1.522, respectively.

IV. CALCULATION OF DENSITY

A tentative plot of density against number of carbon atoms for the alkylbenzenes showed that (*1*) the density decreases slightly with increasing carbon content; (*2*) the mono-*tert*-alkylbenzenes have consistently higher densities than other monoalkylbenzenes and most polyalkylbenzenes; (*3*) *o*-dialkylbenzenes and polyalkylbenzenes with two adjacent alkyl groups have a similar exaltation in density; (*4*) polyalkylbenzenes with more than one pair of adjacent alkyl groups have a further increase in density proportional to the number of such pairs. Thus 1,2,3-trialkyl- and 1,2,4,5-tetraalkyl-benzenes have twice as much increase in density; 1,2,3,4-tetraalkylbenzenes have three times as much, etc.

All of these effects are correlated by the following simple equation:

$$d_4^{20} = 0.850 + (0.12/n)(1 + a + b)$$

in which n is the number of carbon atoms, a is the number of pairs of adjacent alkyl groups, and b is 1 for mono-*tert*-alkylbenzenes and zero for other aromatics, even including those with tertiary alkyl groups.

Ninety-six of the more reliable observations of density are plotted in figure 1 with the densities adjusted for a and b (when applicable). This group includes the selections of the Bureau of Standards for hydrocarbons up to C_{10} (7, 8); several for higher aromatics accompanied by precise melting points, a property which is considered a criterion of purity; and also some others with concordant observations by different investigators. For clarity the points are represented by letters suggestive of the type of hydrocarbon, as shown in the legend. The less reliable observations show a similar distribution of points, but are omitted to avoid too great congestion of the graph.

The curve is the plot of the equation, $d = 0.850 + 0.12/n$, the base line being the asymptote. No reliable observation on density of an alkylbenzene disagrees with the values thus calculated by more than 0.01, and none for a *n*-alkylbenzene by more than 0.002. No further consistent deviation of a sub-class (same letter) is apparent. On the other hand, when many more accurate data become available, further refinement in the calculations will be possible. Values of density

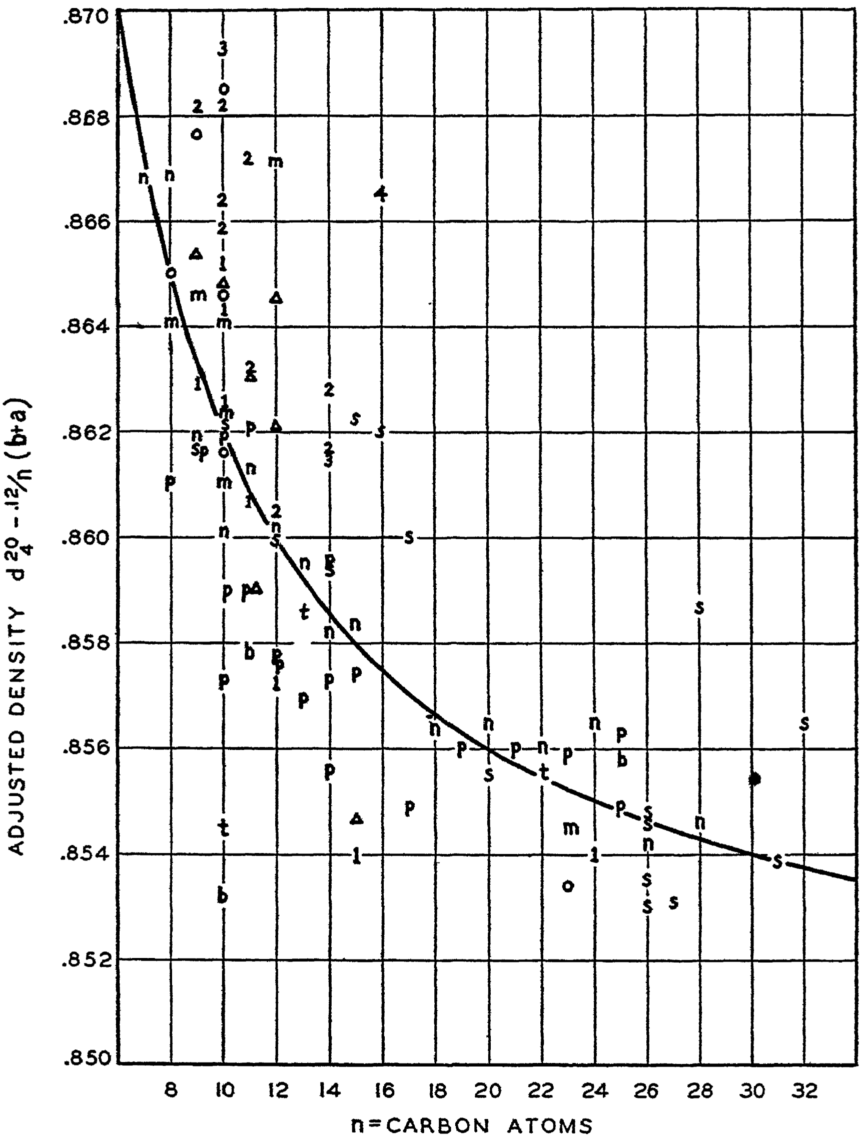

FIG. 1. Density

b, branched-chain primary monoalkylbenzenes
m, *m*-dialkylbenzenes
n, *n*-monoalkylbenzenes
o, *o*-dialkylbenzenes
p, *p*-dialkylbenzenes
s, *sec*-monoalkylbenzenes
t, *tert*-monoalkylbenzenes
Δ, 1,3,5-trialkylbenzenes
1, polyalkylbenzenes with one pair of adjacent alkyl groups
2, polyalkylbenzenes with two pairs of adjacent alkyl groups
3, polyalkylbenzenes with three pairs of adjacent alkyl groups (vicinal tetraalkyl)
4, polyalkylbenzenes with four pairs of adjacent alkyl groups (pentaalkyl)

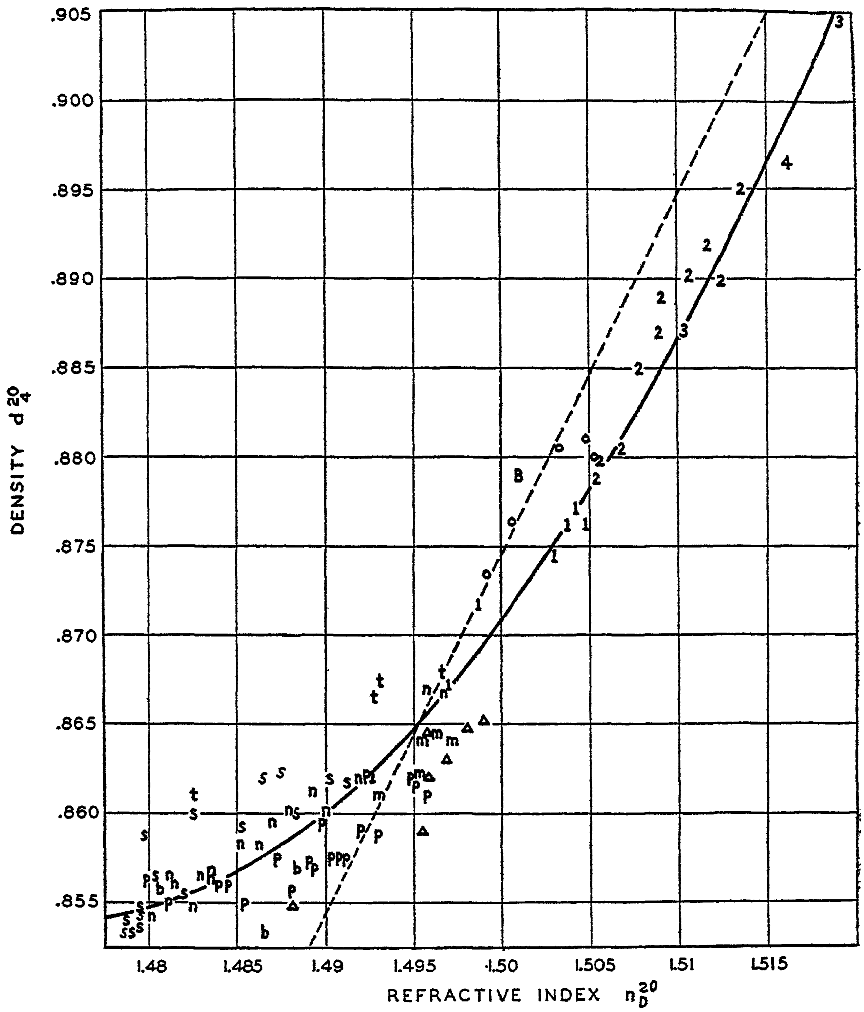

Fig. 2. Density *versus* refractive index

B, benzene
b, branched-chain primary monoalkyl benzenes
m, *m*-dialkylbenzenes
n, *n*-monoalkylbenzenes
o, *o*-dialkylbenzenes
p, *p*-dialkylbenzenes
s, *sec*-monoalkylbenzenes
t, *tert*-monoalkylbenzenes
Δ, 1,3,5-trialkylbenzenes
1, polyalkylbenzenes with one pair of adjacent alkyl groups
2, polyalkylbenzenes with two pairs of adjacent alkyl groups
3, polyalkylbenzenes with three pairs of adjacent alkyl groups (vicinal tetraalkyl)
4, polyalkylbenzenes with four pairs of adjacent alkyl groups (pentaalkyl)

calculated by this relation are listed in the table when the observations are missing for both density and refractive index, or when they differ from the calculations by more than 0.01 and 0.006, respectively.

V. RELATION BETWEEN DENSITY AND REFRACTIVE INDEX

Figure 2 is the plot of refractive index against density for the same group of 96 aromatics by classes as in figure 1. The points seem to be clustered to some extent about the parabola which is the plot of the equation,

$$d_4^{20} - 0.854 = 27(n_D^{20} - 1.475)^2$$

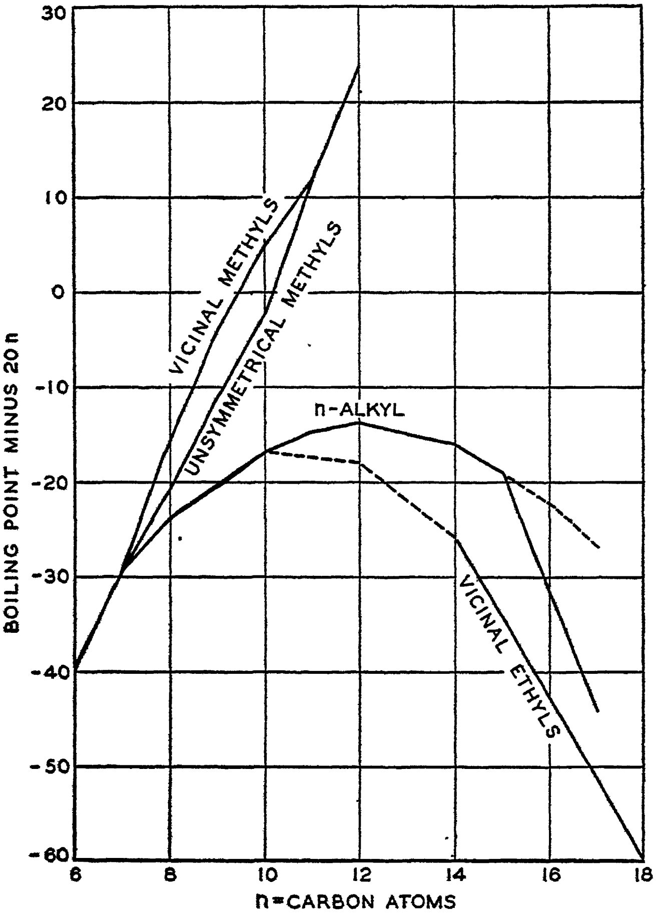

FIG. 3. Boiling point

especially if added weight is assigned to the *n*-alkylbenzenes, as before. However, the more symmetrical hydrocarbons, the 1,3,5-trialkylbenzenes, and the *p*- and to a less extent the *m*-dialkylbenzenes, have densities lower by 0.002 to 0.004 than the others. On the other hand, several branched-chain monoalkylbenzenes have reported densities about 0.01 higher than the curve, but are not shown because the values are not supported by other studies and are not consistent among themselves. The "refractivity intercept" line (dotted line in the figure) of Ward and Kurtz (382) holds well except for those hydrocarbons of low refractive index, which include mostly those of high boiling point.

The curve is used to calculate values of refractive index in the table when observations are missing or questionable (deviating more than 0.006 from the calculations). It is used also to calculate density values from observed refractive index values when the former are missing or questionable and the latter are more consistent.

VI. BOILING POINTS

A plot of boiling point against number of carbon atoms, such as used by Schmidt (302) for *n*-alkylbenzenes only, is necessarily on such a small scale that moderate discrepancies are not apparent. In order to accentuate them, figures 3 to 5 are plotted with the ordinates "boiling point minus *kn*", a procedure which permits a much larger scale. Straight lines connecting the observations are used instead of smooth curves, thus identifying the points and making it unnecessary to have several different kinds of points. When observations are lacking, or so far out of line that their reliability is questioned, dotted lines are used connecting calculated (interpolated or extrapolated) values.

Figure 3 shows convex "curves" for normal alkylbenzenes, and for the ethylbenzenes with all ethyl groups adjacent (1,2,3-triethylbenzene is not reported in the literature). The boiling point reported for *n*-hendecylbenzene is 17°C. lower than that extrapolated. The observed boiling points of the *n*-alkylbenzenes agree well with the equation

$$\text{b.p.} = 18n + 21 - 1800/n^2$$

as shown in the following table:

n	BOILING POINT		n	BOILING POINT	
	Calculated	Observed		Calculated	Observed
6	79.0	80.1	11	204.1	205.3
7	110.3	110.6	12	224.5	226.2
8	136.9	136.2	13	244.35	244
9	160.8	159.2	14	263.8	264
10	183.0	183.3	15	283.0	282

For extrapolation above C_{15} it may be necessary to revise the equation to contain an n^2 term. For the vicinal ethylbenzenes no equation is satisfactory, partly because of the small number of reliable points.

The polymethylbenzenes show nearly a straight line:

$$\text{b.p.} = 30n - 100$$

It is curious that toluene and pentamethylbenzene have boiling points a little low for the vicinal series, and a little high for the unsymmetrical series. They can be considered to belong to both classes. The symmetrical polymethylbenzenes, *p*-xylene, mesitylene, and durene (not shown), would have points just below the line for unsymmetrical isomers.

Boiling points of four other series of monoalkylbenzenes are plotted in figure 4. The "C_2 chain" series includes ethylbenzene, cumene, and *tert*-butylbenzene, each of which has two carbon atoms in the longest arrangement of its side chain. The lines agree fairly well with the following equations:

C_2 chain	b.p. = $16.5n + 4$
Isoalkyl	b.p. = $21n - 37$
2-Phenylalkane (secondary)	b.p. = $20n - 27$
2-Phenyl-2-methylalkane (tertiary)	b.p. = $19n - 21$

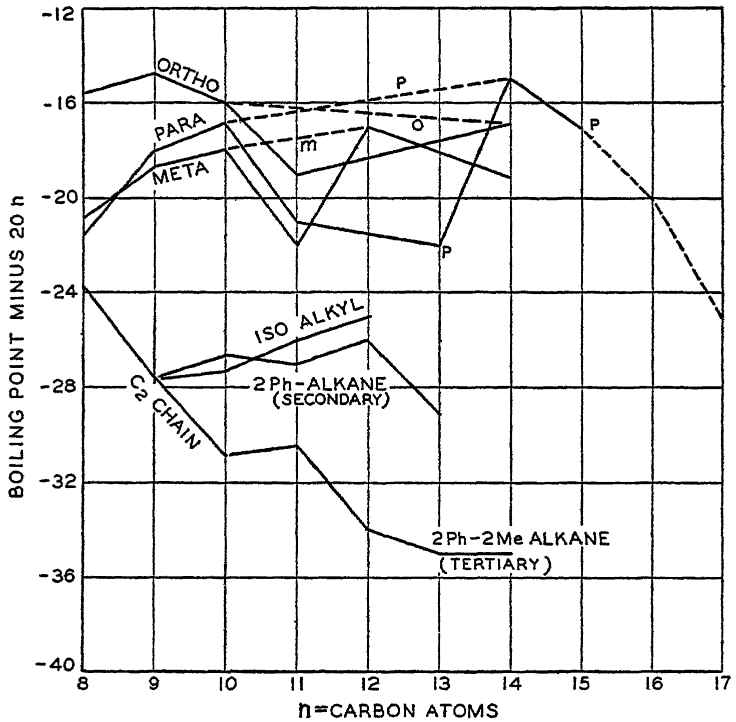

FIG. 4. Boiling points of monoalkylbenzenes and methyl-*n*-alkylbenzenes

In view of the large scale it is uncertain whether discrepancies from straight lines are real or due to inaccuracies. For more highly branched monoalkylbenzenes it seems advisable to deduct 3°C. for each additional branch from the estimates by the above equations.

Figure 4 also shows the three series of methyl-*n*-alkylbenzenes. Dips in the "curves" seem to indicate that the reported boiling points for the C_{11} and C_{13} members are about 4°C. low. There is very little difference between the *m*- and *p*-isomers, and the *o*-isomer also differs only when the second alkyl group is methyl or ethyl. The equation for an average corrected curve for this series is

$$\text{b.p.} = 17n + 33 - 1800/n^2$$

Figure 5 includes other meta and para di-*n*-alkylbenzenes. An upward revision of about 5°C. is suggested for the boiling point of "1-ethyl-3-*n*-propylbenzene"

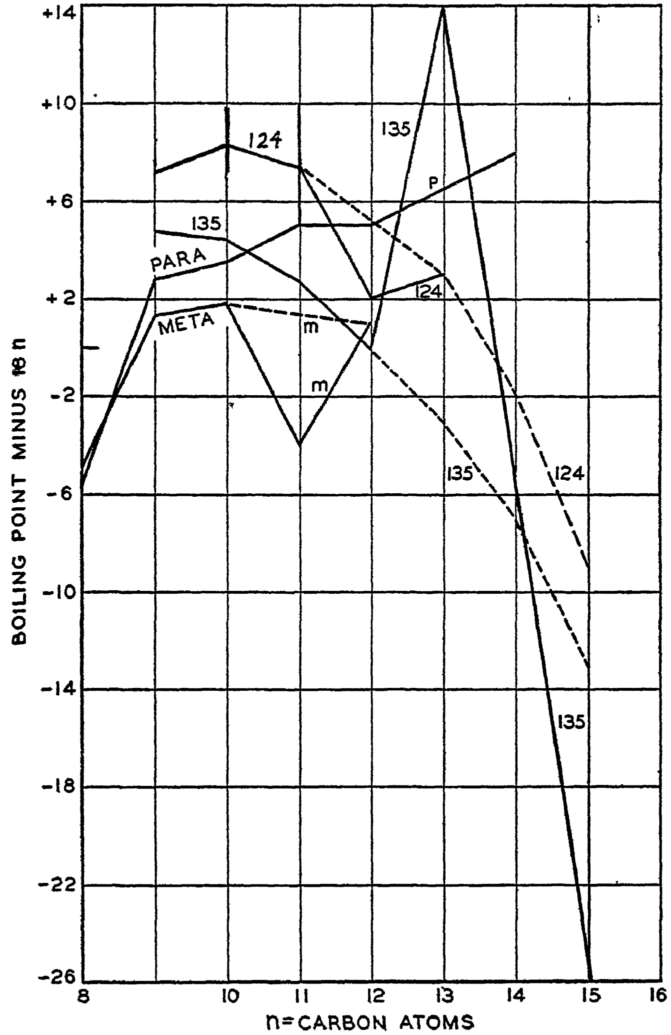

FIG. 5. Boiling points of di- and tri-*n*-alkylbenzenes

(probably wrong structure). These series are represented approximately by the equation:

$$\text{b.p.} = 17n + 31 - 1800/n^2$$

The symmetrical series (1,3,5-tri-*n*-alkylbenzenes) shows much more violent fluctuations, which can be smoothed out by an adjustment for the C_{13} and C_{15} members. The unsymmetrical series (1,2,4-) requires only one slight adjustment (C_{12}). The short vertical lines at C_{10} and C_{11} are drawn to indicate three and four isomers, respectively, included in the class. The "curve" is drawn through the average boiling point of such isomers. The following equations are applicable:

1,3,5-Tri-*n*-alkylbenzene..............................	b.p. = $12.5n + 78 - 1800/n^2$
1,2,4-Tri-*n*-alkylbenzene..............................	b.p. = $12.5n + 82 - 1800/n^2$

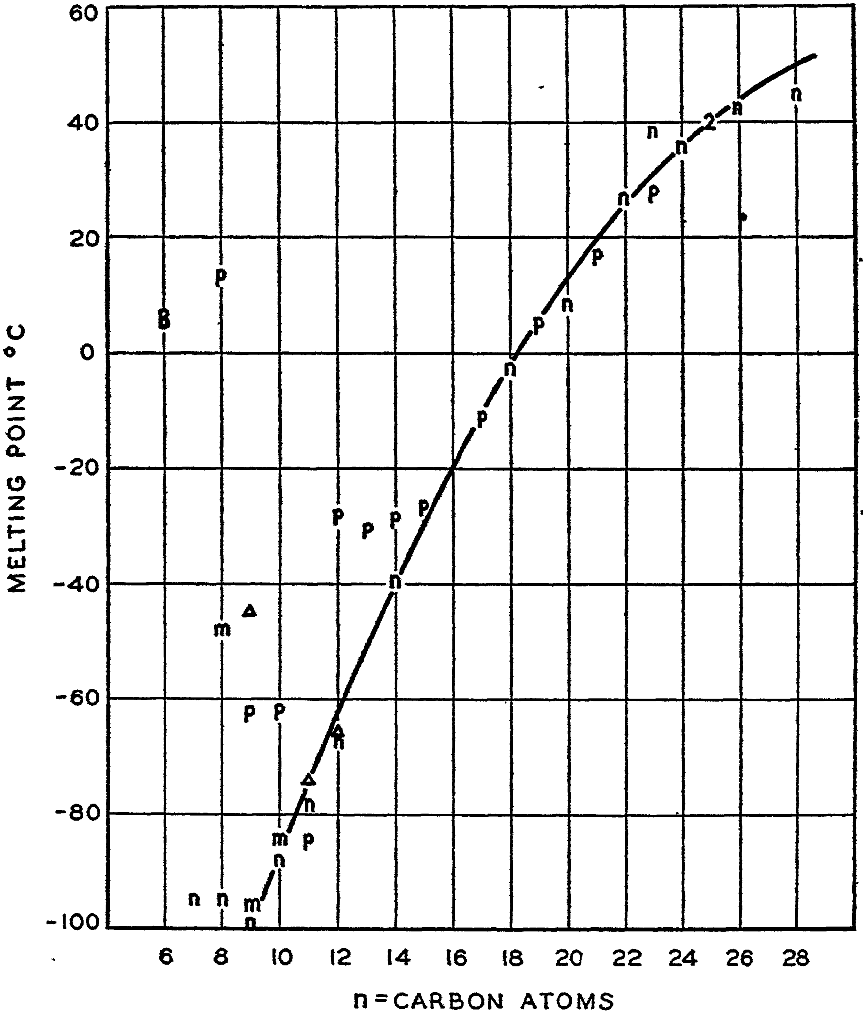

FIG. 6. Melting point. B, benzene; m, *m*-di-*n*-alkylbenzenes; p, *p*-methyl-*n*-alkylbenzenes; Δ, 1,3,5-tri-*n*-alkylbenzenes; 2, hexadecylmesitylene.

Still another series, the hexaalkylbenzenes, is not shown because it would require an individual graph. The members with reliable observations, those with

12, 17, 18, and 24 carbon atoms, have observed boiling points consistent with the equation:

$$\text{b.p.} = 5n + 216 - 1800/n^2$$

Estimates for boiling points of alkylbenzenes not so far included are based on the following approximate relations, which are superposed on results from the most appropriate equations for di- or tri-*n*-alkylbenzenes (tetra- and penta-alkylbenzenes are derived from the latter):

(*1*) The boiling points of isomeric poly-*n*-alkylbenzenes are nearly alike except for a correction for adjacent methyl and ethyl groups. Each such pair of methyl groups adds about 7°C., and an adjacent methyl and ethyl group add about 4°C. to the boiling point.

(*2*) One branch in any alkyl group lowers the boiling point about 10°C.; a second branch lowers it about half as much; a third branch, half as much again, etc.

Estimates are listed in table 1 for boiling points when the observations are missing or differ from the calculations by more than 5°C., for all known alkylbenzenes up to C_{16} and a few beyond, and for the 18 unknown C_{11} alkylbenzenes.

VII. MELTING POINTS

Melting points of organic compounds are usually extremely sensitive to structure, so that comparatively few of the observations on 138 of the alkylbenzenes can be correlated quantitatively. In figure 6 are plotted the "best" observations on all the known members of four series of *n*-alkylbenzenes. A single curve, a parabola, which is the plot of the equation,

$$\text{m.p.} = 19n - 0.3n^2 - 247$$

agrees well with the values for mono-*n*-alkyl and the *m*-di-*n*-alkyl series above C_8, the symmetrical series above C_9, and the methyl-*p*-*n*-alkylbenzenes above C_{14}. Most of the latter were observed by Schmidt and Schoeller (305), who were aware of the discrepancies for the members with 12, 13, and 14 carbon atoms, so that they are probably real as are those for the members below C_{11}. Single observations on melting points of *n*-octylbenzene (3) and 1-methyl-4-*n*-octylbenzene (223) are questionable because they are about 30°C. higher than those of other observers which are consistent with the curve.

The apparent validity of one curve for those series has permitted the estimation of twelve melting points not yet observed. For the other observations the only correlation now possible seems to be the qualitative one that high symmetry, as in hexaalkylbenzenes, results in high melting points.

VIII. SUMMARY

Table 1 presents a summary of data on the boiling points, density, refractive index, and melting points of benzene and alkylbenzenes.

The author is indebted to Dr. C. F. Feasley, who checked the section dealing with the discussion of identity, and to other colleagues for helpful suggestions.

TABLE 1

Properties of benzene and alkylbenzenes

FORMULA	HYDROCARBON	BOILING POINT		d_4^{20}	n_D^{20}	MELTING POINT	REFERENCES
		°C.	mm.			°C.	
C_6H_6	Benzene	80.103	760	0.87903 1.015 (solid at 0°C.)	1.50110	5.53	(7, 78, 103, 120, 128, 328, 392)
C_7H_8	Toluene	110.623	760	0.86683	1.49682	−95.00	(7, 103, 120, 128, 328, 392)
C_8H_{10} (4 possible)	Ethylbenzene	136.187	760	0.86696	1.49580	−95.00	(7, 103, 120, 128, 311, 328, 392)
	o-Xylene	144.414	760	0.88005	1.50524	−25.15	(7, 103, 120, 121, 128, 329, 392)
	m-Xylene	139.102	760	0.86412	1.49715	−47.87	(7, 103, 128, 329, 392)
	p-Xylene	138.348	760	0.86100 1.052 (solid at 0°C.)	1.49580	13.27	(7, 78, 103, 120, 121, 128 329, 392)
C_9H_{12} (8 possible; all known)	*n*-Propylbenzene	159.216	760	0.86198	1.4919	−99.50 (I) −101.53 (II)	(7, 103, 120, 128, 147, 271, 302, 304, 328, 351, 372, 392)
	Isopropylbenzene (cumene)	152.393	760	0.86175	1.4913	−96.00	(7, 103, 120, 128, 147, 271, 328, 362, 392)
	1-Methyl-2-ethylbenzene	165.23	760	0.8810	1.5048	−80.84 (I) −86.53 (II)	(7, 121, 147, 351)
	1-Methyl-3-ethylbenzene	161.29	760	0.8645	1.4961	−95.59 (I) −97.0 (II)	(7, 121, 147, 351, 372)
	1-Methyl-4-ethylbenzene	161.94	760	0.8616	1.4952	−62.36	(7, 121, 147, 291, 351, 372)
	1,2,3-Trimethylbenzene (hemimellitene)	176.10	760	0.8951	1.5139	−25.39	(7, 128, 147, 329, 351)

	1,2,4-Trimethylbenzene (pseudocumene)	169.18	760	0.8762	1.5048	−43.79 (I) −48.98 (II)	(7, 128, 131a, 147, 267, 271, 329, 351)
	1,3,5-Trimethylbenzene (mesitylene)	164.64	760	0.8653	1.4990	−44.73 (I) −49.80 (II) −51.68 (III)	(7, 128, 147, 271, 329, 351)
$C_{10}H_{14}$ (22 possible; all known)	*n*-Butylbenzene	183.26	760	0.8601	1.4900	−87.97	(8, 38B, 45, 50, 93, 121, 128, 131a, 142, 204, 267, 302, 304, 328, 344, 350, 352)
	sec-Butylbenzene	173.30	760	0.8618	1.4900	−75.47	(8, 23, 38B, 50, 128, 131a, 142, 188, 189, 204, 221, 237, 326, 328, 349, 352, 362, 368)
	Isobutylbenzene	172.80	760	0.8532	1.4865	−51.48	(8, 38b, 50, 121, 128, 142, 308, 328, 352)
	tert-Butylbenzene	169.10	760	0.8662	1.4925	−57.85	(8, 32, 38b, 50, 57, 128, 131a, 142, 143, 153, 218, 237, 267, 308, 322, 323, 325, 326, 328, 343, 352, 368)
	1-Methyl-2-*n*-propylbenzene	184	760	0.8736	1.4993		(8, 12, 15, 38b, 67, 93, 96, 174, 227)
	1-Methyl-3-*n*-propylbenzene	182	760	0.8623	1.4951		(8, 12, 15, 38b, 67, 96, 227, 320?, 372)
	1-Methyl-4-*n*-propylbenzene	183.45	760	0.8588	1.4930	−62	(8, 12, 15, 38b, 93, 96, 161 227, 305, 320?, 372)
	1-Methyl-2-isopropylbenzene (*o*-cymene)	178.5	760	0.8766	1.5006	−71.6	(8, 12, 38b, 82, 96, 227, 297)

TABLE 1—*Continued*

FORMULA	HYDROCARBON	BOILING POINT		$^{20}_{4}$	n^{20}_{D}	MELTING POINT	REFERENCES
		°C.	mm.			°C.	
$C_{10}H_{14}$ (continued)	1-Methyl-3-isopropylbenzene (*m*-cymene)................	175.2	760	0.8610	1.4930	−63.8	(8, 12, 38b, 96, 119, 227, 297, 320?)
	1-Methyl-4-isopropylbenzene (*p*-cymene	177.23	760	0.8567	1.4908	−68.17	(8, 12, 38b, 96, 120, 127, 143, 201, 204, 215, 218, 227, 237, 245, 267, 271, 287, 297, 306, 326, 329, 379, 381, 384, 393)
	o-Diethylbenzene.............	183.5	760	0.8790	1.5034	−32.07	(8, 38b, 114, 137, 178)
	m-Diethylbenzene............	181.62		0.8641	1.4955	−84.09	(8, 38b, 69, 120, 245, 258, 350, 372)
	p-Diethylbenzene.............	183.8	760	0.8620	1.4950	−42.95	(8, 15, 38b, 161, 178, 193, 213, 222, 245)
	1,2-Dimethyl-3-ethylbenzene...	193.91	760	0.8921	1.5117	−49.5	(8)
	1,2-Dimethyl-4-ethylbenzene...	189.75		0.8745	1.5031	−67.0	(8, 17?, 211, 373, 381)
	1,3-Dimethyl-2-ethylbenzene...	190.01		0.8904	1.5107	−16.3	(8, 77a, 337)
	1,3-Dimethyl-4-ethylbenzene...	188.41		0.8763	1.5038	−63.0	(8, 193, 260, 282, 337)
	1,3-Dimethyl-5-ethylbenzene...	183.75		0.8648	1.4981	−84.2	(8, 118, 260, 261, 287)
	1,4-Dimethyl-2-ethylbenzene...	186.91		0.8772	1.5043	−53.7	(8, 111, 193, 287, 337)
	1,2,3,4-Tetramethylbenzene (prehnitene)	205.04		0.9053	1.52013	−6.25	(8, 68, 229, 233, 267, 329, 331, 332, 337, 338, 339)
	1,2,3,5-Tetramethylbenzene (isodurene)	197.92	760	0.8899	1.5125	−23.97	(8, 68, 229, 267, 329, 331, 339)
	1,2,4,5-Tetramethylbenzene (durene)...	196	760	0.889† 1.032 (solid)	1.512†	79.3	(8, 68, 85, 100, 112, 113, 211, 229, 245, 267, 329, 331, 339)

$C_{11}H_{16}$ (51 possible; 33 known)	*n*-Amylbenzene	205.3	760	0.8613	1.4892	−78.25	(38a, 45, 49, 79, 81, 93, 123, 125, 167, 175, 176, 204, 217, 227, 272, 285, 302, 304, 307, 317, 321, 328, 347, 350, 355, 356, 357, 394)
	2-Phenylpentane	193	760	0.8597	1.4856		(79, 81, 112, 155, 156, 163, 167, 188, 189, 263, 315, 322, 349, 353, 360, 361, 368)
	3-Phenylpentane	191	760	0.8649	1.4880		(76, 81, 156, 167, 190, 225, 322?, 343)
	1-Phenyl-2-methylbutane (benzylbutane)	194	760	0.8617	1.4880		(43, 92, 123, 129, 167, 220, 293, 347, 355, 356, 357)
	1-Phenyl-3-methylbutane (isoamylbenzene)	196	760	0.8558	1.4847		(38, 64, 66?, 93, 123, 167, 191, 236, 296, 307, 314, 315, 328, 350, 367?)
	2-Phenyl-2-methylbutane (*tert*-amylbenzene)	189.6	760	0.8675	1.4930		(9, 10, 55, 97, 112, 143, 150, 153, 156, 159, 165, 167, 206, 217, 227, 245, 263, 283, 308, 322, 323, 343, 361, 370)
	2-Phenyl-3-methylbutane	189	760	0.8641	1.4913		(130, 155, 165, 167, 190, 206, 283, 308?)
	1-Phenyl-2,2-dimethylpropane (neopentylbenzene)	186	760	0.8569	1.4884		(56, 57, 167, 183, 283, 364)
	1-Methyl-2-*n*-butylbenzene	201	760	0.8721	1.4958		(227, 250)
	1-Methyl-3-*n*-butylbenzene	198? (203)‡	760	0.8640	1.4924	(−74)‡	(59, 137, 227, 250)
	1-Methyl-4-*n*-butylbenzene	199? (204)‡	760	0.8590	1.4920	−85? (−74)‡	(227, 234, 250, 305, 319)
	(1-Methyl-2-*sec*-butylbenzene)§	(193)‡	760	(0.872)‡	(1.501)‡		Unknown
	1-Methyl-3-*sec*-butylbenzene	197		(0.865)‡	1.4957		(23, 131, 318)

TABLE 1—*Continued*

FORMULA	HYDROCARBON	BOILING POINT		d_4^{20}	n_D^{20}	MELTING POINT	REFERENCES
		°*C.*	*mm.*			°*C.*	
$C_{11}H_{16}$ (continued)	1-Methyl-4-*sec*-butylbenzene	200		0.8650	1.4932		(23, 143, 237, 318, 326, 379, 384)
	(1-Methyl-2-isobutylbenzene)§	(193)‡	760	(0.872)‡	(1.501)‡		Unknown
	(1-Methyl-3-isobutylbenzene)§	(195)‡		(0.861)‡	(1.492)‡		(94; unknown, see text)
	(1-Methyl-4-isobutylbenzene)§	(193)‡	760	(0.861)‡	(1.492)‡		Unknown, see text
	1-Methyl-2-*tert*-butylbenzene	171? (188)‡		(0.863)‡	1.4930		(207)
	1-Methyl-3-*tert*-butylbenzene	188	760	(0.863)‡	1.4928		(25, 133, 180, 205, 257, 318, 370)
	1-Methyl-4-*tert*-butylbenzene	193		0.8621	1.4921		(11, 31, 37, 58, 143, 150, 205, 207, 213, 215, 218, 237, 257, 265a, 323, 326, 371, 377, 384)
	(1-Ethyl-2-*n*-propylbenzene)§	(204)‡	760	(0.872)‡	(1.501)‡		Unknown
	1-Ethyl-3-*n*-propylbenzene?	194? (199)‡		0.8580	(1.487)‡		(288); probably unknown, see text
	1-Ethyl-4-*n*-propylbenzene	203	760	0.866	(1.496)‡	(−74)‡	(29, 161, 390)
	(1-Ethyl-2-isopropylbenzene)§	(193)‡		(0.872)‡	(1.501)‡		Unknown
	1-Ethyl-3-isopropylbenzene	195		0.8616	(1.492)‡	<−20	(29, 108, 353)
	1-Ethyl-4-isopropylbenzene	197		0.8625	1.4927	<−20	(29, 193, 287, 353, 379, 384)
	(1,2-Dimethyl-3-*n*-propylbenzene)§	(215)‡	760	(0.883)‡	(1.508)‡		Unknown
	1,2-Dimethyl-4-*n*-propylbenzene	204		0.8670	1.4972	<−20	(17, 373)
	(1,3-Dimethyl-2-*n*-propylbenzene)§	(208)‡		(0.883)‡	(1.508)‡		Unknown
	1,3-Dimethyl-4-*n*-propylbenzene	208		0.8778	1.5010	<−20	(36, 251, 373)

	1,3-Dimethyl-5-*n*-propylbenzene	209		(0.861)‡	1.4933		(168, 251, 373)
	1,4-Dimethyl-2-*n*-propylbenzene	207		(0.872)‡	(1.501)‡	<−20	(373)
	(1,2-Dimethyl-3-isopropylbenzene)§	(203)‡		(0.883)‡	(1.508)‡		Unknown
	1,2-Dimethyl-4-isopropylbenzene	199		0.8710	1.4980	−41	(179, 192, 198, 211)
	(1,3-Dimethyl-2-isopropylbenzene)§	(198)‡		(0.883)‡	(1.508)‡		Unknown
	1,3-Dimethyl-4-isopropylbenzene	195		0.869	1.5018	<−80	(179, 251, 373)
	1,3-Dimethyl-5-isopropylbenzene	191		0.859	1.4955	−55.3	(179, 213?, 251, 380)
	(1,4-Dimethyl-2-isopropylbenzene)§	(196)‡		(0.872)‡	(1.501)‡		Unknown
	(1-Methyl-2,3-diethylbenzene)§	(208)‡		(0.883)‡	(1.508)‡		Unknown
	(1-Methyl-2,4-diethylbenzene)§	(205)‡		(0.872)‡	(1.501)‡		Unknown
	1-Methyl-2,5-diethylbenzene	207		(0.872)‡	(1.501)‡		(232)
	(1-Methyl-2,6-diethylbenzene)§	(209)‡		(0.883)‡	(1.508)‡		Unknown
	1-Methyl-3,4-diethylbenzene	203		(0.872)‡	(1.501)‡		(213)
	1-Methyl-3,5-diethylbenzene	200.70		0.8631	1.4969	−74.12	(108?, 118, 120, 261, 353, 372?)
	(1,2,3-Trimethyl-4-ethylbenzene)§	(223)‡	760	(0.894)‡	(1.514)‡		Unknown
	(1,2,3-Trimethyl-5-ethylbenzene)§	(219)‡		(0.883)‡	(1.508)‡		Unknown
	1,2,4-Trimethyl-3-ethylbenzene	216		0.899	1.5133	<−50	(336, 337)

TABLE 1—*Continued*

FORMULA	HYDROCARBON	BOILING POINT		d_4^{20}	n_D^{20}	MELTING POINT	REFERENCES
		°C.	*mm.*			*°C.*	
$C_{11}H_{16}$ (continued)	1,2,4-Trimethyl-5-ethylbenzene	210		0.885	1.5079	−13.6	(12, 15, 17, 193, 287?, 336, 353, 365)
	(1,2,4-Trimethyl-6-ethylbenzene)§	(216)‡	760	(0.883)‡	(1.508)‡		Unknown
	1,3,5-Trimethyl-2-ethylbenzene	210		0.8856	1.5090	−15.56	(12, 15, 77a, 115, 172, 187, 193, 287, 336, 353, 366)
	Pentamethylbenzene	231.9	760	0.921†? (0.9045)‡ 1.011 (solid)	1.5287†? (1.519)‡	54.3	(2, 17, 45a, 68, 85, 99, 100, 113, 169, 229, 269, 329, 338, 339, 378, 395)
$C_{12}H_{18}$ (136 possible; 55 known)	*n*-Hexylbenzene	226.2	760	0.8602	1.4879	−66.8	(45, 78a, 80, 81, 123, 124, 175, 176, 182, 272, 296, 302, 304, 317, 321, 328, 385)
	2-Phenylhexane	214	760	0.8600	1.4882		(47, 124, 156, 221, 349, 361)
	3-Phenylhexane	211		0.8609	1.4877		(4, 124, 221, 344)
	1-Phenyl-2-methylpentane	215		0.8624	1.4847		(39, 92, 348)
	1-Phenyl-3-methylpentane	221		0.8605	1.4876		(181, 195, 293, 348, 355, 357)
	1-Phenyl-4-methylpentane	218		0.8536	(1.48)‡		(307, 347)
	2-Phenyl-2-methylpentane	206		0.8717	1.4938		(153, 156, 309)
	2-Phenyl-3-methylpentane	211		0.8798? (0.860)‡	1.4973? (1.490)‡		(156, mixture with 3-phenyl-3-methylpentane)
	2-Phenyl-4-methylpentane	198? (210)‡	760	0.8592	1.4856		(33?, 156, 191)

3-Phenyl-2-methylpentane.....	209	760	0.8678	1.4912		(4, 157)
3-Phenyl-3-methylpentane.....	206		0.8755	1.4958		(153, 309)
1-Phenyl-2-ethylbutane (3-benzylpentane)	218		(0.860)‡	(1.490)‡		(347)
(1-Phenyl-2,2-dimethylbutane)§..................	215	760	0.8592	1.4878		(355, 357; unknown, see text)
1-Phenyl-2,3-dimethylbutane...	217		0.8718	(1.501)‡		(64)
2-Phenyl-2,3-dimethylbutane...	210		0.8814? (0.870)‡	1.4988		(153)
2-Phenyl-3,3-dimethylbutane...	206	760	0.8803? (0.866)‡	1.4962		(156)
1-Methyl-2-*n*-amylbenzene.....	(224)‡	760	0.8725	(1.501)‡		(227)
1-Methyl-3-*n*-amylbenzene.....	223		0.8593	1.4911		(60, 227)
1-Methyl-4-*n*-amylbenzene.....	99	12	0.8569	1.4904	−28	(227, 305)
	(224)‡	760				
1-Methyl-4-(1′-methylbutyl)-benzene....................	95	20	0.8631	1.4920		(384)
	(214)‡	760				
1-Methyl-4-(ethylpropyl)benzene........................	85	13	0.8694	1.4940		(143)
	(214)‡	760				
1-Methyl-2-isoamylbenzene.....	(213)‡		0.8675	(1.497)‡		(227)
1-Methyl-3-isoamylbenzene.....	(211)‡		0.8565	(1.484)‡		(227)
1-Methyl-4-isoamylbenzene.....	211		0.8629	1.4950	< −20	(38, 227, 319)
1-Methyl-3-*tert*-amylbenzene....	209		0.8673	(1.497)‡	< −20	(213?, 371)
1-Methyl-4-*tert*-amylbenzene...	208		0.8711	1.4952		(122, 143, 371)
1-Methyl-3-(1′, 2′-dimethylpropyl)benzene	200–205	760	(0.860)‡	(1.490)‡		(98)
1-Methyl-4-(1′,2′-dimethylpropyl)?-benzene...........	207	760	0.8661	1.4951		(213?, 371)
1-Ethyl-4-*sec*-butylbenzene.....	86	16	0.8629	1.4921		(384)
	(212)‡	760				
1-Ethyl-3-*tert*-butylbenzene....	205		(0.860)‡	(1.490)‡		(25, 27)

TABLE 1—*Continued*

FORMULA	HYDROCARBON	BOILING POINT		d_4^{20}	n_D^{20}	MELTING POINT	REFERENCES
		°C.	mm.			°C.	
$C_{12}H_{18}$ (continued)	1-Ethyl-4-*tert*-butylbenzene.....	211		0.8635	1.4950		(31, 77, 257, 265a)
	1,3-Di-*n*-propylbenzene........	217		0.9124? (0.862)‡	1.4928	(−62)‡	(18, 132?, 179, 372)
	1,4-Di-*n*-propylbenzene........	221	760	0.8564	1.4914		(16, 18, 101, 132?, 179, 203, 287a, 324?)
	1-*n*-Propyl-4-isopropylbenzene........................	215	760	0.8614	1.4972		(35, 101, 270)
	1,2-Diisopropylbenzene........	203.75	760	0.87007	1.49603	−56.68	(141?, 235b, 353?, 374?)
	1,3-Diisopropylbenzene...	203.18		0.85593	1.48883	−63.13	(34, 88, 119, 177, 248, 320, 353, 374)
	1,4-Diisopropylbenzene...	210.37	760	0.85676	1.48983	−17.07	(58?, 141, 160, 163, 185, 230, 235b, 237, 248, 263, 326, 327, 368, 374?)
	1,3-Dimethyl-4-*n*-butylbenzene........................	96 (219)‡	8 760	0.8718	1.4992		(255)
	1,3-Dimethyl-4-*sec*-butylbenzene...	84 (210)‡	8 760	0.8650	1.4959		(253, 255)
	1,3-Dimethyl-5-*sec*-butylbenzene.....	98 (206)‡	15 760	0.8621	1.4940		(255)
	1,3-Dimethyl-4-isobutylbenzene......	96 (210)‡	15 760	0.8694	1.4994		(255)
	1,2-Dimethyl-4-*tert*-butylbenzene........................	210		(0.867)‡	1.4970		(252, 257)
	1,3-Dimethyl-4-*tert*-butylbenzene........................	213		0.9452? (0.870)‡	1.5098? (1.499)‡		(54, 255, 340)

1,3-Dimethyl-5-*tert*-butylbenzene	206	760	0.8645	1.4958	−21.5	(25, 26, 40, 53, 58, 78a, 218, 228, 253, 255, 256, 257, 261, 262, 265a, 340)
1,4-Dimethyl-2-*tert*-butylbenzene	210	760	(0.870)‡	(1.499)‡		(257)
1-Methyl-3-ethyl-6-*n*-propylbenzene	215? (219)‡		0.8762	(1.503)‡		(232)
1-Methyl-2-ethyl-4-isopropylbenzene	214	760	0.8673	1.4969		(44, 65, 192, 198, 376)
1-Methyl-3-ethyl-4-isopropylbenzene	213	760	0.8722	1.5006		(13)
1,2,4-Triethylbenzene	217.72		0.8791	1.4982	<−70	(87, 186, 193, 353)
1,3,5-Triethylbenzene	215.92		0.8621	1.4958	−66.48	(84, 108?, 118, 120, 131a, 134, 164, 186, 193, 194, 214, 258, 259, 260, 261, 287, 333, 342, 372?, 381)
1,2,4-Trimethyl-5-*n*-propylbenzene	228	760	0.887	1.5095		(148)
1,3,5-Trimethyl-2-*n*-propylbenzene	221		0.8782	1.5033	<−20	(187, 199, 366)
1,2,4-Trimethyl-5-isopropylbenzene	223		0.8802	1.5069	21	(14, 179)
1,3-Dimethyl-4,6-diethylbenzene	105 (224)‡	15 760	(0.880)‡	(1.506)‡	<−20	(282)
1,4-Dimethyl-2,5-diethylbenzene	105 (224)‡	15 760	0.8803	1.5091		(111)
Hexamethylbenzene	263.8		1.042 (solid)	1.5032 (solid)	165.3	(2, 28, 77a, 85, 113, 132, 147a, 169, 226, 229, 245, 267, 268, 269, 280, 329, 332, 338, 339, 363, 395)

TABLE 1—*Continued*

FORMULA	HYDROCARBON	BOILING POINT		d_4^{20}	n_D^{20}	MELTING POINT	REFERENCES
		°*C.*	*mm.*			°*C.*	
$C_{13}H_{20}$ (335 possible; 58 known)	*n*-Heptylbenzene	244	760	0.8595	1.4875	(−51)‡	(45, 96, 124, 175, 176, 208, 227, 287, 296, 302, 304, 317, 353, 375, 385)
	2-Phenylheptane	231	760	0.8610	1.4863	−32	(86, 212, 360, 361)
	3-Phenylheptane	227		0.8607	1.4862		(86, 139, 221, 293)
	4-Phenylheptane	224		0.8665	1.4872		(86, 156)
	2-Phenyl-2-methylhexane	225		0.8737	1.4943		(153, 156)
	2-Phenyl-3-methylhexane	225		0.8804? (0.866)‡	1.4961		(156, binary mixture with 3-phenyl-3-methylhexane)
	2-Phenyl-5-methylhexane	223	760	0.8659	(1.496)		(188)
	3-Phenyl-2-methylhexane 3-Phenyl-5-methylhexane } ?	225	760	0.8691	1.4895		(156, ternary mixture with 2-phenyl-5-methylhexane)
	3-Phenyl-3-methylhexane	226	760	0.8776	1.4980		(138, 153, 156)
	1-Phenyl-2-ethylpentane (3-benzylhexane)	120 (236)‡	24 760	(0.859)‡	(1.488)‡		(92)
	1-Phenyl-3-ethylpentane	110 (226)‡	10 760	(0.859)‡	(1.488)‡		(42, 81?)
	3-Phenyl-3-ethylpentane	226		0.8679	1.4965		(55, 57, 153, 309)
	1-Phenyl-4,4-dimethylpentane	115 (233)‡	9 760	0.9443? (0.859)‡	1.5274? (1.488)‡		(146)
	2-Phenyl-2,3-dimethylpentane	223	760	0.8801? (0.867)‡	1.4966		(153)
	2-Phenyl-2,4-dimethylpentane	218	760	0.869	1.4926		(152, 153, 309)
	2-Phenyl-4,4-dimethylpentane? 3-Phenyl-2,2-dimethylpentane? } ?	223	760	0.8757? (0.863)‡	1.4934		(156, mixture)

3-Phenyl-2,3-dimethylpentane..	226	760	0.8803? (0.868)‡	1.4974		(153)
3-Phenyl-2,4-dimethylpentane..	225	760	0.8747? (0.859)‡	1.507? (1.489)‡		(247)
2-Phenyl-2,3,3-trimethylbutane	226	760	0.8867? (0.874)‡	1.5019		(153)
1-Methyl-2-*n*-hexylbenzene....	238	760	(0.868)‡	(1.498)‡		(243)
1-Methyl-3-*n*-hexylbenzene.....	238		(0.859)‡	(1.489)‡		(243)
1-Methyl-4-*n*-hexylbenzene.....	238? (243)‡		0.8569	1.4890	−30.5	(243, 305)
1-Methyl-4-(1′-ethylbutyl)benzene (3-*p*-tolylhexane).......	165 (233)‡	135 760	0.8575	1.4910		(344))
1-Ethyl-4(1′-methylbutyl)-benzene.....................	97 (231)‡	11 760	0.8626	1.4910		(384)
1-Ethyl-4-*tert*-amylbenzene.....	200–230 (226)‡		(0.859)‡	(1.489)‡		(122)
1-*n*-Propyl-3-*n*-butylbenzene...	238		(0.856)‡	1.4837		(244)
1-Isopropyl-2-*tert*-butylbenzene.	210? (225)‡		(0.868)‡	(1.498)‡		(22)
1-Isopropyl-3-*tert*-butylbenzene.	222		0.8512	1.4832		(22, 218a, contains about 9 per cent mono-*tert*-heptylbenzene)
1-Isopropyl-4-*tert*-butylbenzene.	224		0.8610	1.4928		(20, 21, 22)
1,3-Dimethyl-4-*n*-amylbenzene	124 (234)‡	16 760	(0.868)‡	1.4972		(254)
1,3-Dimethyl-5-*n*-amylbenzene	106 (230)‡	10 760	(0.859)‡	(1.489)‡		(254)
1,3-Dimethyl-4-(1′-methylbutyl)benzene	103 (224)‡	11 760	(0.866)‡	1.4959		(254)
1,3-Dimethyl-4-(ethylpropyl)-benzene....................	106 (224)‡	13 760	(0.868)‡	1.4973		(254)
1,3-Dimethyl-4-(2′-methylbutyl)benzene	111 (224)‡	13 760	(0.864)‡	1.4942		(254)

TABLE 1—*Continued*

FORMULA	HYDROCARBON	BOILING POINT		d_4^{20}	n_D^{20}	MELTING POINT	REFERENCES
		°C.	mm.			°C.	
$C_{13}H_{20}$ (continued)	1,3-Dimethyl-5-(2′-methylbutyl)benzene	108 (220)‡	15 760	(0.859)‡	(1.488)‡		(254)
	1,3-Dimethyl-4-isoamylbenzene	232		0.8867? (0.867)	1.4966		(38, 254)
	1,3-Dimethyl-5-isoamylbenzene	108 (223)‡	15 760	(0.859)‡	(1.488)‡		(254)
	1,3-Dimethyl-4-*tert*-amylbenzene	94 (219)‡	14 760	(0.868)‡	(1.498)‡		(254)
	1,3-Dimethyl-5-*tert*-amylbenzene	103 (215)‡	14 760	(0.868)‡	1.4982		(253, 254)
	1,3-Dimethyl-4-(1′,2′-dimethylpropyl)benzene	102 (219)‡	13 760	(0.874)‡	1.5022		(254)
	1,3-Dimethyl-4-neopentylbenzene	98 (219)‡	10 760	(0.868)‡	1.5081? (1.498)‡		(254)
	1-Methyl-3-ethyl-6-*n*-butylbenzene	237		0.8795	(1.506)‡		(232)
	1-Methyl-3-ethyl-6-isobutylbenzene	229		0.8795	(1.506(‡		(232)
	1-Methyl-3,5-di-*n*-propylbenzene	248? (230)‡		(0.859)‡	(1.489)‡	(−51)‡	(168, 372?)
	1-Methyl-2-*n*-propyl-4-isopropylbenzene	225.2		0.8650	1.4937		(66, 192)
	1-Methyl-2,4-diisopropylbenzene	225	760	0.8664	1.499		(83, 185?)

	1-Methyl-2,6-diisopropylbenzene	228		0.8768	1.5032		(82)
	1-Methyl-3,5-diisopropylbenzene	218		0.8668	1.4955		(108, 215, 306, 326?)
	1,3-Diethyl-4-isopropylbenzene	226					(105)
	1,3?-Diethyl-5?-isopropylbenzene	256? (228)‡	760	(0.868)‡ (0.868)‡	(1.498)‡ (1.498)‡		(213)
	1,3,5-Trimethyl-2-*n*-butylbenzene	241		(0.878)‡	(1.505)‡		(187)
	1,3,5-Trimethyl-2-isobutylbenzene	230		0.8767	1.4995		(199)
	1,2,3-Trimethyl-5-*tert*-butylbenzene	115 (226)‡	17 760	(0.880)‡	1.5049		(115)
	1,2,4-Trimethyl-6-*tert*-butylbenzene	92 (226)‡	3.5 760	0.878)‡	(1.505)‡	32.5	(61)
	1,3,5-Trimethyl-2,4-diethylbenzene	236? (246)‡		(0.896)‡	(1.515)‡		(281)
	Pentamethylethylbenzene	(270)‡		(0.915)‡	(1.524)‡	125	(68)
$C_{14}H_{22}$ (871 possible; 57 known)	*n*-Octylbenzene	264	760	0.8572	1.4849	−37.0	(3, 81?, 93, 96, 266, 279, 290, 296, 300, 302, 304, 310, 383)
	2-Phenyloctane	125 (253)‡	20 760	0.8580	1.4850	−38.9	(144, 274, 275, 300, 359, 360, 361, 368)
	4-Phenyloctane	119 (253)‡	18 760	0.859	(1.488)‡		(221)
	1-Phenyl-2-methylheptane	130 (257)‡	16 760	(0.859)‡	(1.488)‡		(43)

TABLE 1—*Continued*

FORMULA	HYDROCARBON	BOILING POINT		d_4^{20}	n_D^{20}	MELTING POINT	REFERENCES
		°C.	mm.			°C.	
$C_{14}H_{22}$ (continued)	1-Phenyl-6-methylheptane	250		(0.859)‡	(1.488)‡	<−20	(264)
	2-Phenyl-2-methylheptane	244		0.8756	1.4951		(154)
	3-Phenyl-3-methylheptane	121	17	0.8738	1.4932		(144, 151)
		(245)‡	760				
	4-Phenyl-4-methylheptane	243		0.8704	1.4920		(138, 151)
	3-Phenyl-3-ethylhexane	239		0.875	1.4943		(138, 151)
	3-Phenyl-4-ethylhexane	206?	760	(0.859)‡	(1.488)‡		(4, 286)
		(250)‡					
	2-Phenyl-2,3-dimethylhexane	237	760	0.8861?	1.4961		(154)
				(0.866)‡			
	2-Phenyl-2,4-dimethylhexane	239	760	0.8729	1.4920		(154)
	2-Phenyl-2,5-dimethylhexane	238		0.8749	1.4939		(138, 154)
	3-Phenyl-2,3-dimethylhexane	238		0.8763	1.4958		(151)
	3-Phenyl-3,4-dimethylhexane	114	10	0.8757	1.4929		(151)
		(242)‡	760				
	3-Phenyl-3,5-dimethylhexane	116	10	0.8750	1.4918		(151)
		(242)‡	760				
	1-Phenyl-2-*n*-propylpentane (4-benzylheptane)	244		0.8496?	1.4844		(246)
				(0.856)‡			
	2-Phenyl-2-methyl-3-ethylpentane	237	760	0.8782?	1.4942		(154)
				(0.864)‡			
	3-Phenyl-2-methyl-3-ethylpentane	239	760	0.8816?	1.4981		(151)
				(0.868)‡			
	2-Phenyl-2,3,3-trimethylpentane	235	760	0.8939?	1.5031?		(154)
				(0.867)‡	(1.497)‡		
	2-Phenyl-2,4,4-trimethylpentane	235	760	0.8803?	1.4938		(154, 218a?)
				(0.863)‡			

3-Phenyl-2,2,3-trimethylpentane	259?	760	(0.867)‡	(1.497)‡		(151)
	(239)‡					
3-Phenyl-2,3,4-trimethylpentane	237		0.8808?	1.4970		(151, 152)
			(0.867)‡			
1-Methyl-2-*n*-heptylbenzene	263	760	0.8717	1.4951		(96)
1-Methyl-3-*n*-heptylbenzene	261		0.8615	1.4913	(−40)‡	(96)
1-Methyl-4-*n*-heptylbenzene	265		0.8573	1.4891	−28.5	(96, 305)
1,4-Di-*n*-butylbenzene	260		0.8556	1.4881	−24	(142, 235, 241)
1-*n*-Butyl-4-*sec*-butylbenzene	251		0.8570	1.4885		(142)
1-*n*-Butyl-4-isobutylbenzene	252		0.8508	1.4858		(142)
1-*n*-Butyl-4-*tert*-butylbenzene	249		0.8595	1.4898	−46	(142)
1,3-Di-*sec*-butylbenzene	90	3	(0.859)‡	1.4890		(23)
	(245)‡	760				
1,4-Di-*sec*-butylbenzene	239	760	0.8590	1.4892	−58	(51, 102?, 142, 160, 230, 237, 368, 384)
1-*sec*-Butyl-4-isobutylbenzene	242	760	0.8511	1.4856		(142)
1-*sec*-Butyl-4-*tert*-butylbenzene	236		0.8607	1.4892		(142)
1,4-Diisobutylbenzene	243		0.8456?	1.4834?	−21	(142)
			(0.859)‡	(1.488)‡		
1-Isobutyl-4-*tert*-butylbenzene	239	760	0.8457?	1.4875		(142)
			(0.859)‡			
1,3-Di-*tert*-butylbenzene	106.5	18.2	(0.858)‡	1.4870	10.6	(48?, 172a, 213?, 313?)
	(241)‡	760				
1,4-Di-*tert*-butylbenzene	237		(0.860)‡	1.4904†	77.8	(26, 41, 52, 142, 143, 153, 160, 162, 202, 204, 213, 230, 235a, 237, 294, 313, 322, 323, 325, 326, 341, 368, 377)
1,3-Dimethyl-4-*n*-hexylbenzene	133	13	0.886?	1.4972		(104)
	(248)‡	760	(0.867)‡			
1,3-Dimethyl-4-(1′-ethylbutyl)-benzene	102	3	0.8645	1.493		(344)
	238	760				

TABLE 1—*Continued*

FORMULA	HYDROCARBON	BOILING POINT		d_4^{20}	n_D^{20}	MELTING POINT	REFERENCES
		°C.	mm.			°C.	
$C_{14}H_{22}$ (continued)	1,2?-Dimethyl-3?-(2′-ethylbutyl)benzene	113 (259)‡	12 760	0.9022? (0.884)‡	1.5082		(102a)
	1-Methyl-3-ethyl-6-isoamylbenzene	246		0.8733	(1.502)‡		(232)
	1-Methyl-4-isopropyl-2-*n*-butylbenzene	235		0.8897? (0.867)‡	(1.497)‡		(66)
	1-Methyl-4-isopropyl-2-isobutylbenzene	230	760	0.9136? (0.867)‡	(1.497)‡		(66)
	1-Methyl-2-isopropyl-5-*tert*-butylbenzene	236	760	(0.867)‡	(1.497)‡		(20, 21)
	1-Methyl-3?-isopropyl-4-*tert*-butylbenzene	231	760	(0.867)‡	(1.497)‡		(20, 21)
	1-Methyl-3-isopropyl-5-*tert*-butylbenzene	228	760	0.8660	1.4950		(19, 21)
	1-Methyl-3-isopropyl-6-*tert*-butylbenzene	238	760	(0.867)‡	(1.497)‡		(20, 21)
	1-Methyl-4-isopropyl-2-*tert*-butylbenzene	238	760	(0.867)‡	(1.497)‡		(19, 22)
	1-Methyl-4-isopropyl-3-*tert*-butylbenzene	228	760	0.8839? (0.867)‡	1.4972		(19, 22, 126)
	1-Ethyl-3,5?-diisopropylbenzene	228	760	0.8610	1.4918		(90)
	1,3,5-Trimethyl-2-(3′-methylbutyl)benzene	243		0.8776	1.4992		(199)

	1,3-Dimethyl-2-ethyl-5-*tert*-butylbenzene	125	20	(0.877)‡	1.5044		(115)
		(237)‡	760				
	1-Methyl-2,6-diethyl-4-isopropylbenzene	245		0.8810? (0.868)‡	1.498		(369)
	1,2,3,4-Tetraethylbenzene	254	760	0.8873	1.5101	<−50	(117, 170, 271, 334, 335)
	1,2,3,5-Tetraethylbenzene	249		0.8799	1.5056	−21	(333, 334)
	1,2,4,5-Tetraethylbenzene	248		0.8788	1.5054	10	(164? 171, 193, 333, 334 353, 362, 372?)
$C_{15}H_{24}$ (2217 possible; 23 known)	*n*-Nonylbenzene	282	760	0.8584	1.4863	(−29)‡	(81?, 175, 176, 204, 242, 296, 317, 328, 385)
	2-Phenylnonane	147	19	0.8627	1.4875		(359, 360, 361)
		(273)‡	760				
	5-Phenylnonane	127	12	0.8586	1.4868		(275)
		(273)‡	760				
	1-Phenyl-5-methyloctane 1-Phenyl-5-ethylheptane } ?	271		0.8857? (0.858)‡	1.5020? (1.487)‡		(81, mixture)
	4-Phenyl-4-ethylheptane	128	15	0.8698	1.4900		(138)
		(264)‡	760				
	3-Phenyl-3,6-dimethylheptane	123	14	0.8760	1.4959		(138)
		(261)‡	760				
	3-Phenyl-5-methyl-3-ethylhexane	242		0.8696	1.4888		(138)
	3-Phenyl-2,4-dimethyl-3-ethylpentane?	253	760	0.8746	1.4940		(152)
	1-Methyl-4-*n*-octylbenzene	283	760	0.8574	1.4872	−23	(223, 291, 292, 305)
	1-Methyl-4-(1′-methylheptyl)-benzene	116	7	0.8607	1.4877		(384)
		(270)‡	760				
	1-Methyl-4-(1′,5′-dimethylhexyl)benzene (2-methyl-6-*p*-tolylheptane)	136	15	0.8488	1.4815		(174?, 295)
		(265)‡	760				

TABLE 1—*Continued*

FORMULA	HYDROCARBON	BOILING POINT		d_4^{20}	n_D^{20}	MELTING POINT	REFERENCES
		°C.	mm.			°C.	
$C_{15}H_{24}$ (continued)	1-Isopropyl-4-(3′-methylamyl)benzene	266	760	0.8602	1.4897		(196)
	1-*tert*-Butyl-2-*tert*-amylbenzene	243		0.8645	1.4885		(218a; contains 87 per cent *tert*-octylbenzene)
	1,3-Dimethyl-5-(triethylmethyl)benzene	259	760	(0.858)‡	(1.487)‡		(24)
	1-Methyl-4-isopropyl-2-isoamylbenzene	245		0.887?			(66)
				(0.866)‡	(1.496)‡		
	1-Methyl-2,4?-di-*tert*-butylbenzene	247	760	0.9044?	1.5158?		(215)
				(0.866)‡	(1.496)‡		
	1-Methyl-3,5?-di-*tert*-butylbenzene	244	760	(0.858)‡	(1.487)‡	32	(26, 58, 59, 213, 257)
	1,2,4-Tri-*n*-propylbenzene	135	20	(0.865)‡	1.4950		(18, 324?)
		(261)‡	760				
	1,3,5-Tri-*n*-propylbenzene	133	20	(0.858)‡	(1.487)‡	(−29)‡	(18, 132?)
		(257)‡	760				
	1,2,4-Triisopropylbenzene	244		0.8620	1.4924		(34, 48, 160, 185, 237, 248, 327)
	1,3,5-Triisopropylbenzene	238	760	0.8547	1.4882	−15	(34, 88, 135, 136, 248)
	1,3,5-Trimethyl-2,4,6-triethylbenzene	247?		(0.906)‡	(1.519)‡		(281)
		(283)‡					
$C_{16}H_{26}$ (5749 possible; 19 known)	*n*-Decylbenzene?	293?	760	0.8805?	1.4970?		(81)
		(302)‡		(0.858)‡	(1.486)‡		
	2-Phenyldecane	132	3	0.8620	1.4864		(144, 359, 360, 361)
		(293)‡	760				

1-Phenyl-6-methylnonane 1-Phenyl-6-ethyloctane ?	289? (299)‡		0.8809? (0.858)‡	1.4988? (1.480)‡		(81, mixture)
1-Phenyl-3,7-dimethyloctane	275		0.8722? (0.862)‡	1.4919		(197)
4-Phenyl-4-*n*-propylheptane	141 (283)‡	15 760	0.8694	1.4902		(138)
4-Phenyl-2,4,6-trimethylheptane	144 (277)‡	18 760	0.8753? (0.863)‡	1.4930		(138)
1-Methyl-4-*n*-nonylbenzene	161 (298)‡	12 760	(0.858)‡	(1.487)‡	<−20 (−20)‡	(140)
1-Ethyl-4-(1′-methylheptyl)benzene	126 (286)‡	7 760	0.8609	1.4874		(384)
1,3-Di-*sec*?-amylbenzene	265		0.8522	1.4830	<−75	(108?, 316, 360)
1,4-Di-(1′-methylbutyl)benzene	265		0.8619	1.4880		(263, 368, 384)
1,3-Di-*tert*?-amylbenzene	265		0.8727? (0.858)‡	1.4948? (1.487)‡	<−20	(10, 75)
1,4-Di-*tert*-amylbenzene	265	760	0.8526	1.4862		(263, 322, 323)
1,3-Dimethyl-5?-*n*-octylbenzene	(271)‡		(0.858)‡	(1.487)‡	−66	(274)
1,3,5-Trimethyl-2-*n*-heptylbenzene	272	760	0.8732	1.4958		(199)
1-Methyl-2,4,6-triisopropylbenzene	253? (261)‡		0.8695	1.4994	<−20	(83, 91)
Diethyldiisopropylbenzene (probably a mixture)	257		0.8686	1.4986	<−50	(90)
Pentaethylbenzene	277	760	0.8965	1.5166	<−20	(85, 99, 170, 333, 335, 353)
1,3-Dimethyltetraethylbenzene	260? (289)‡		0.8771? (0.903)‡	1.4958? (1.518)‡		(117, 345)

TABLE 1—*Continued*

FORMULA	HYDROCARBON	BOILING POINT		d^{20}_4	n^{20}_D	MELTING POINT	REFERENCES
		°C.	mm.			°C.	
$C_{17}H_{28}$ (14,837 possible; 10 known)	*n*-Hendecylbenzene	296? (313)‡	760	(0.8575)‡	1.4868	(−11)‡	(242)
	2-Phenylhendecane	171	12	0.8600	1.4824	−35	(274, 278, 359, 360, 361)
	2-Phenyl-2-methyldecane	160	20	0.8676	1.4859		(396)
	2-Phenyl-2-methyl-4-ethyl-octane	149	20	0.8620	1.4875		(396)
	4-Phenyl-2-methyl-4-propyl-heptane	144	11	0.8722	1.4932		(138)
	1-Methyl-4-*n*-decylbenzene	169 (316)‡	11	0.8549	1.4854	−11.5	(305)
	1-Ethyl-2,4,5?-triisopropyl-benzene	260? (271)‡	760	(0.871)‡	(1.500)‡	106.9	(91)
	1-Ethyl-2,4,6?-triisopropyl-benzene	256? (271)‡		0.8670	1.4981	−35	(91?, 116)
	1,3,-Dimethyl-2,4,6?-triiso-propylbenzene	276		0.893	1.5105	−25	(91)
	Methylpentaethylbenzene	294	760	(0.900)‡	(1.516)‡	43	(89)
$C_{18}H_{30}$ (38,636 possible; 18 known)	*n*-Dodecylbenzene	185	15	0.8564	1.4838	−3	(124, 158, 175, 176, 177, 266, 274, 277, 302, 303, 304)
	2-Phenyldodecane	184	20	0.8547	1.4822		(124, 144, 303, 368)
	3-Phenyldodecane	171	13	0.8569	1.4837		(124, 303)
	4-Phenyldodecane	164	17	0.8581	1.4852	−24	(124, 274, 279, 303)
	5-Phenyldodecane	158	7.5	0.8589	1.4865		(124, 303)
	6-Phenyldodecane	190	35	0.8570	1.4868		(124, 303)
	1-Phenyl-3-methylhendecane	144	2	0.8618	1.4870		(219)
	5-Phenyl-2,5,8-trimethyl-nonane	155	15	0.8728	1.4913		(138)

	1-Phenyl-5-methyl-3-isoamylhexane (5-benzyl-2,8-dimethylnonane)	150	11	(0.857)‡	(1.485)‡		(46)
	1-Methyl-4-*n*-hendecylbenzene	172	12	(0.857)‡	(1.485)‡	(−2)‡	(140)
	1,4-Di(1′-ethylbutyl)benzene	106	0.3	0.916?	1.5020?		(344)
				(0.857)‡	(1.485)‡		
	1,3-Dimethyl-5?-(2′-methylnonyl)benzene	155–174	10	(0.857)‡	(1.485)‡		(144)
	1,2,4?-Tri-*tert*-butylbenzene	285–305	760	(0.863)‡	(1.493)‡		(160, 162, 202, 213, 218a)
	1,3,5?-Tri-*tert*-butylbenzene	293		(0.857)‡	(1.485)‡	128	(313, 341)
	1,2,4,5-Tetraisopropylbenzene	260?	760	0.850†?		118.4	(34, 48, 58, 91, 102, 132, 160, 185, 202, 248, 327)
		(283)‡		(0.870)‡	(1.50)‡		
	1,2,4-Triethyl-3,6?-diisopropylbenzene	285		0.887	(1.510)‡		(90)
	1,3,5-Triethyl-2,4-diisopropylbenzene	279		0.883	(1.508)‡		(90)
	Hexaethylbenzene	300		0.907† 0.99 (solid)	1.521†	128.3	(5, 34, 48, 85, 90, 99, 110, 117, 132, 134, 170, 202, 217, 245, 301, 333, 353, 395)
$C_{19}H_{32}$ (100,622 possible; 10 known)	*n*-Tridecylbenzene	189	10	(0.856)‡	(1.484)‡	(5)‡	(394)
	2-Phenyltridecane	120	1	(0.855)‡	1.4824		(330)
	7-Phenyltridecane	184	20	0.8541	1.4811	−28.2	(275, 300)
	5-Phenyl-2,8-dimethyl-5-ethylnonane	172	14	0.8945?	1.5053?		(138)
				(0.863)‡	(1.493)‡		
	1-Methyl-4-*n*-dodecylbenzene	155	1.5	0.8560	1.4845	5.0	(305)
	1-Methyl-4-(1′-methylhendecyl)benzene	167	8	0.8594	1.4841		(384)
	1-*n*-Hexyl-4-*n*-heptylbenzene	187	10	(0.856)‡	(1.484)‡	−32	(289)
	1-Methyl-2,4,5?-tri-*tert*-butylbenzene	160–170	4	(0.869)‡	1.584? (1.498)‡		(215)

TABLE 1—*Continued*

FORMULA	HYDROCARBON	BOILING POINT		d_4^{20}	n_D^{20}	MELTING POINT	REFERENCES
		°C.	mm.			°C.	
$C_{19}H_{32}$ (continued)	1-Methyl-2,3,5,6-tetraisopropylbenzene . . .	271? (303)‡	760	0.9111? (0.892)‡	1.5123	10	(91)
	1,3-Diethyl-2,4,6?-triisopropylbenzene	280? (297)‡		0.8837	1.5051	−65	(91)
$C_{20}H_{34}$ (263,381 possible; 5 known)	*n*-Tetradecylbenzene. . .	196	9	0.8565	1.4836	8.6	(124, 175, 176, 177, 302, 304)
	2-Phenyltetradecane..	188	7	0.8555	1.4820	−7	(276)
	5-Phenyl-2,8-dimethyl-5-*n*-propylnonane...	181	15	0.8677	1.4855		(138)
	1-Ethyl-4-(1′-methylhendecyl)-benzene...	173	7	0.8586	1.4852		(384)
	?-Diheptylbenzene.........	165	9	0.854	1.4839		(360)
$C_{21}H_{36}$ (690,709 possible; 4 known)	5-Phenyl-2,8-dimethyl-5-isobutylnonane.	173	11	0.8982? (0.861)‡	1.5042? (1.491)‡		(138)
	1-Methyl-4-*n*-tetradecylbenzene..	170	0.8	0.8560	1.4839	16.8	(305)
	1,2,4?-Triamylbenzene.. . ..	312–318	760	0.867	1.497		(160, 316)
	1,3,5?-Triamylbenzene...	282–288	760	(0.856)‡	(1.483)‡		(160)
$C_{22}H_{38}$ (1,817,544 possible; 8 known)	*n*-Hexadecylbenzene. . .	237	16	0.8560	1.4814	27	(1, 96, 124, 208, 209, 210, 217, 249, 276, 302, 304, 389)
	2-Phenylhexadecane..	191	6	0.8643	1.4834		(359, 360, 361)

	2-Phenyl-2-methylpentadecane	195	7	0.8611	1.4825	−29	(276)
	4-Phenyl-2-methyl-4-isobutylhendecane	180	6	0.8700	1.4982	−50	(278)
	1-Phenyl-2-*n*-heptylnonane (8-benzylpentadecane)	204	14	(0.855)‡	(1.482)‡		(46)
	?-Di-*sec*-octylbenzene	341	760	(0.855)‡	(1.482)‡		(144, 160)
	1,4?-Di-(3′-methylheptyl)benzene	>190	10	(0.855)‡	(1.482)‡		(144)
	1-Methyl-4-isopropyl-2-*n*-dodecylbenzene	164	1	0.8595	1.4878		(249)
$C_{23}H_{40}$ (4,793,449 possible; 4 known)	*n*-Heptadecylbenzene			(0.855)‡	(1.481)‡	38? (32)	(394)
	1-Methyl-2-*n*-hexadecylbenzene	239	15	0.8604	(1.490)‡	9	(209)
	1-Methyl-3-*n*-hexadecylbenzene	237	15	0.8557	(1.483)‡	12	(209)
	1-Methyl-4-*n*-hexadecylbenzene	240	15	0.8548	(1.480)‡	27.5	(209)
$C_{24}H_{42}$ (12,675,741 possible; 10 known)	*n*-Octadecylbenzene	249	15	0.8565	1.4816	36	(1, 125a, 145, 204, 208, 210, 216, 217, 238, 240, 312, 354, 375, 383, 389)
	9-Phenyloctadecane	150	0.08	0.8744? (0.857)‡	1.4862		(297a)
	2-Phenyl-2-methylheptadecane	190	9	0.8870? (0.860)‡	1.5096? (1.490)‡	−40	(278)
	5-Phenyl-5-*n*-butyltetradecane	185	6	0.8559	1.4814	−48	(279)
	1-Phenyl-2,2-dimethylhexadecane			(0.855)‡	(1.481)‡	−19	(273)
	2-Phenyl-2,4-dimethylhexadecane	182	3	(0.856)‡	1.4825		(330)
	1-Phenyl-12-*n*-propylpentadecane	153.5	0.1	(0.854)‡	1.4781		(342b)

TABLE 1—*Concluded*

FORMULA	HYDROCARBON	BOILING POINT		d_4^{20}	n_D^{20}	MELTING POINT	REFERENCES
		°C.	mm.			°C.	
$C_{24}H_{42}$ (continued)	?-Dinonylbenzene	152–163	5	(0.855)‡	(1.481)‡		(160)
	1,3-Dimethyl-4-*n*-hexadecylbenzene	250	15	0.858b†	(1.487)‡	33.5	(209, 210)
	Hexa-*n*-propylbenzene	332	760	0.871b†	(1.500)‡	103	(132)
$C_{25}H_{44}$ (6 known)	4-Phenyl-13-*n*-propylhexadecane	147.5	0.08	(0.855)‡	1.4813		(342b)
	1-Phenyl-3-*n*-octylhendecane (9-(2′-phenylethyl)heptadecane)	189	1	0.8560	1.4806	−26.7	(298, 299, 300)
	1-Methyl-4-(1′-methylheptadecyl)benzene (2-*p*-tolyloctadecane)	237	8	0.8563	1.4798		(384)
	1-Methyl-4-(1′-octyldecyl)-benzene (9-*p*-tolyloctadecane)	185	1	0.8551	1.4811	<−40	(74, 298, 299, 300)
	1,2,4-Trimethyl-5-*n*-hexadecylbenzene	224	2	0.8782	1.4977	−50	(276)
	1,3,5-Trimethyl-2-*n*-hexadecylbenzene	258	15	0.858†	(1.487)‡	40	(209, 210)
$C_{26}H_{46}$ (10 known)	1-Phenyleicosane	212	1	0.8544†	1.4801†	43	(299, 300, 317a, 342a, 387)
	2-Phenyleicosane	204.5	1	0.8550†	1.4795	29.0	(299, 300, 388)
	3-Phenyleicosane	202	1	0.8549†	1.4796	29.3	(298, 299, 300, 388)
	4-Phenyleicosane	199	1	0.8548†	1.4794	31.4	(299, 300, 388)
	5-Phenyleicosane	197	1	0.8548†	1.4796	30.2	(276, 298, 299, 300, 388)
	7-Phenyleicosane	196	1	0.8537	1.4794	16.4	(298, 299, 300, 388)
	9-Phenyleicosane	196	1	0.8532	1.4790	17.9	(298, 299, 300, 388)
	1-Methyl-4-(1′-*n*-heptyldodecyl)benzene (8-*p*-tolylnonadecane)	195	1	0.8530	1.4808	8.7	(300)

	1,4?-Di-*sec*-decylbenzene.......	230	10	(0.855)‡	(1.481)‡		(144)
	?-Tetraamylbenzene....	340–390	760	0.89? (0.864)‡	(1.494)‡		(316)
$C_{27}H_{48}$	11-Phenylheneicosane.	204	1	0.8533	1.4788	20.8	(74, 298, 299, 300, 386)
$C_{28}H_{50}$ (4 known)	1-Phenyldocosane....	247	4	0.8547	1.4825	44	(238, 239)
	5-Phenyldocosane.......... . .	201	1	0.8587	1.4796	38	(238, 240)
	11-Benzylheneicosane..........	211	1	0.8544	1.4838	−2.1	(46, 300)
	1,3-Dimethyl-4,6?-di(2′-methylnonyl)benzene... ..	>234	10	(0.863)‡	(1.493)‡		(144)
$C_{30}H_{54}$	?-Di-*sec*-dodecylbenzene..	>241	10	(0.854)‡	(1.48)‡		(144, 160)
	?-Tri-*sec*-octylbenzene.... ..	>176	1	(0.854)‡	(1.48)‡		(144)
$C_{31}H_{56}$	13-Phenylpentacosane..... ..	235	1	0.8541† 0.95 (solid)	1.4787	33	(269, 298, 299, 300)
$C_{32}H_{58}$	5-Phenylhexacosane........ . .	255	4	0.8565	1.4806	33	(238, 239)
$C_{38}H_{70}$	1,4-Di-*n*-hexadecylbenzene.....			(0.853)‡	(1.48)‡	53.6	(375, 389)
$C_{41}H_{76}$	18-Phenylpentatriacontane..			0.856†	(1.484)‡	62	(346)
$C_{42}H_{78}$	1,2-Dioctadecylbenzene... ..			0.856†	(1.484)‡	70	(238)
$C_{50}H_{94}$	1,2-Di-(1′-butyloctadecyl)-benzene....			0.850†	(1.48)‡	66	(238)
$C_{60}H_{114}$	Trioctadecylbenzene.....			0.855†	1.4832†	47	(238)

* Roman numerals indicate different crystalline forms.

† Extrapolated value.

‡ Observations in parentheses are calculated.

§ These hydrocarbons are unknown.

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THE CHEMISTRY OF THE RESIN ACIDS

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I. INTRODUCTION

The advance in the chemistry of those organic acids found in the exudates (oleoresins) of many types of pine trees has been rapid. This is probably due to the scientific interest in the difficulty of correctly ascertaining their structures as well as to the commercial interest in developing them as cheap raw materials. Most of the resin acids which have been studied are derived from the pine trees indigenous to Europe and North America. These acids are usually referred to by the term *rosin acids*, rather than by the broader term *resin acids*, which comprehends also those acids obtained from the trees of countries such as New Zealand, Java, and Borneo. Although this chemistry has attracted attention since the early nineteenth century, the major part of resin acid research has occurred during the last twenty-five years.[1]

Since 1936 much important work bearing on the constitution and stereochemical configuration of the resin acids has evolved, and it is the purpose of this paper to clarify the present status of resin acid chemistry in the light of the newer data.

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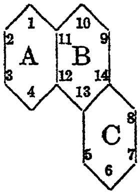
[1] For a review of this subject up to 1937 the reader is referred to L. F. Fieser's *The Chemistry of Natural Products Related to Phenanthrene*, 2nd edition.

II. NOMENCLATURE

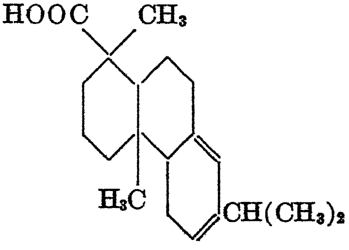
Unfortunately, considerable confusion exists in the naming of the resin acids. In an attempt to minimize the inconvenience of this disorder, an effort has been made to keep the chemical nomenclature of this paper as simple as possible by employing the usage of the modern workers in the field. The ring and nucleus identifications of the resin acids used are as follows:



III. CONSTITUTION

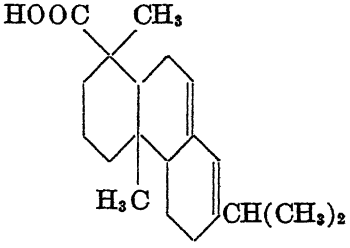
A. Abietic acid

By far the most actively studied rosin acid is the levrorotatory abietic acid, $C_{20}H_{30}O_2$, obtained from pine rosin. By 1932 the tricyclic structure of abietic acid had been conclusively established by selenium dehydrogenation to retene, 1-methyl-7-isopropylphenanthrene, the positions of its two methyl groups had been located, and the presence of two double bonds in the abietic molecule had been reasonably verified. Furthermore, isolation of isobutyric acid from the oxidative cleavage of abietic acid either with permanganate or by ozonolysis, together with the observation that maleic anhydride formed a Diels-Alder adduct with abietic acid, led to a postulation of structure I for abietic acid.



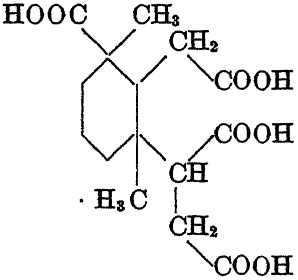
I

This proposed structure, however, can no longer be considered for abietic acid in the light of the discovery made independently by Ruzicka and Bacon (47) and Wienhaus and Sandermann (71) in 1936. These workers found that abietic acid reacts with maleic anhydride only at temperatures above 80°C., whereas *l*-sapietic acid, an unstable rosin acid occurring in pine oleoresin, adds readily to maleic anhydride at room temperature. Inasmuch as both abietic acid and *l*-sapietic acid give the same addition product, the formation of the adduct with abietic acid is the result of an isomerization of abietic acid to *l*-sapietic acid at the higher temperature. Since abietic acid must isomerize to *l*-sapietic acid in order to add maleic anhydride, the conjugated nature of the double bonds in abietic acid is no longer manifest by the formation of the adduct. Comparison of the absorption maximum of abietic acid measured by Kraft (36) with the absorption maxima of polynuclear compounds having conjugated double-bond systems distributed between two rings establishes the probability of conjugation according to structure II. A further indication of conjugation has been obtained by Fieser and Campbell (13), in which the smooth coupling of the diazonium salt of *p*-nitroaniline with abietic acid can be regarded as a positive diagnostic test. This physical and chemical evidence, together with the fact that isobutyric acid is obtained from the oxidation of abietic acid, provides strong support of structure II for abietic acid.



II
Abietic acid

One of the double bonds in abietic acid has been conclusively established at positions 9,14 as in structure II by Ruzicka and Sternbach (58) through the oxidative degradation of α-tetrahydroxyabietic acid (60). On the basis of Ruzicka's earlier oxidation work on abietic acid itself (53), from which the tricarboxylic acid (IV) is formed, the tetracarboxylic acid isolated from the two-step oxidation of α-tetrahydroxyabietic acid with lead tetraacetate and sodium hypobromite can only have structure III. The final chemical evidence for structure II was obtained in 1941 with almost unequivocal proof for the location of the second double bond of abietic acid at the 7,8-position by Ruzicka, Sternbach, and Jeger (63). The diketo acid (V) was prepared from iodotrihydroxyabietic acid by oxidation and removal of the iodine atom with hydriodic acid, followed by conversion to azadehydroabietic acid (VII). This synthesis was carried out by treating V with ammonia; the dihydropyridine (VI) was presumably formed,



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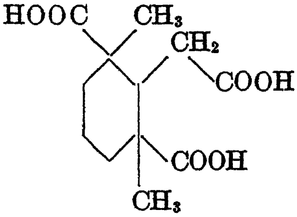
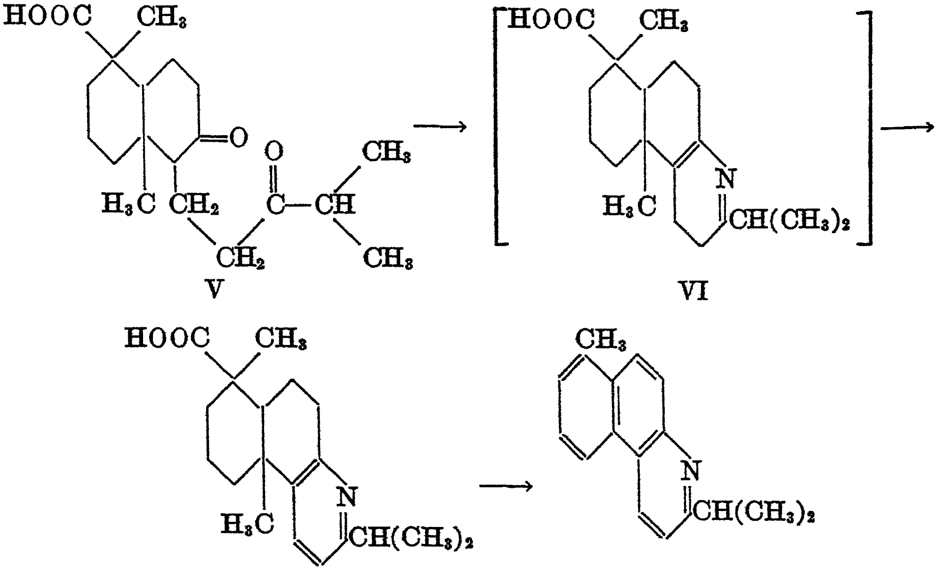


IV

which disproportionated and/or dehydrogenated to VII. From selenium dehydrogenation of VII the synthetically accessible reference compound, 8-azaretene (VIII) (62), was formed, and the structure of the diketo acid (V) established.



V

VI

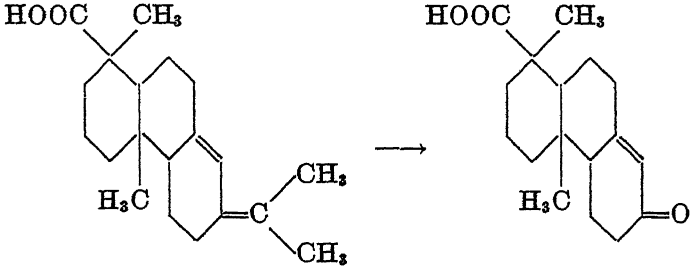
VII

VIII

Confirmatory evidence for structure II is supplied by Woodward's calculations (73) of the absorption spectra for normal conjugated dienes (the double bonds not lying in one ring). $\lambda_{max.}$ (calculated) for structure II is 242 μ ± 5 μ and $\lambda_{max.}$ (observed) for abietic acid is 237.5 μ (36).

It is evident from the various constants reported in the literature that abietic acid contains an impurity. Early workers used an abietic acid having melting points ranging from 154°C. to 166°C. and rotations of −60° to −80°. The abietic acid of standard purity used today melts at 170–174°C. and has a rotation of −104°. By purification through its *l*-bornylamine salt Bardyshev (2) has isolated an even purer abietic acid which has a melting point of 174–175°C. and a value for $[\alpha]_D^{22°}$ of −115.6°. It is therefore doubtful whether an absolutely pure sample of abietic acid has yet been prepared.

Some evidence has accumulated regarding this impurity, which presumably is an isomeric rosin acid. Lottermoser and Ghose (44), on titration of an aqueous solution of sodium abietate with hydrochloric acid, observed an unexpected inflection in the titration curve which may be attributed to a rosin acid impurity. More direct evidence as to the nature of the contaminant is given by the isolation in 3 per cent yield of acetone (identified as the 2,4-dinitrophenylhydrazone) from the ozonolysis of abietic acid by Raudnitz, Lederer, and Kahn (46). This isomeric acid, therefore, most probably has structure IX, resulting from equilibrium with structure II of abietic acid.



IX X

More recently Harris (23) has reported the isolation of a rosin acid from pine oleoresin to which structure IX and the name neoabietic acid have been assigned. This acid has a $\lambda_{max.}$ (observed) at 250 μ, in agreement with the $\lambda_{max.}$ (calculated for structure IX) of 252 $\mu \pm 5 \mu$. On ozonolysis acetone is formed and an α,β-unsaturated ketone which has a $\lambda_{max.}$ (observed) at 242 μ in accord with the $\lambda_{max.}$ (calculated) of 239 $\mu \pm 5 \mu$ required by structure X (72). It is quite possible, therefore, that neoabietic acid and the isomeric acid described above are identical.

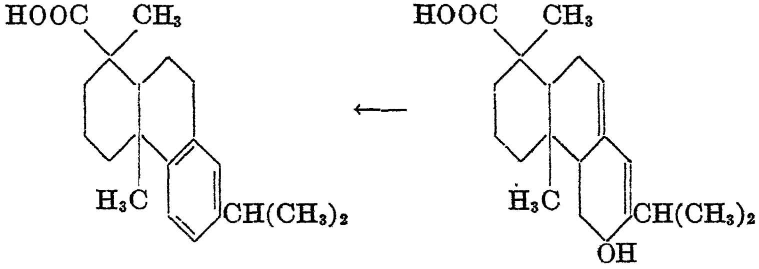
Another new rosin acid of pine oleoresin, isomeric with abietic acid, has been announced by Lombard (40, 42, 43) and given the name *d*-alepic acid, later changed to *d*-sapinic acid. Although a structure has been assigned, no experimental evidence for the structure is yet forthcoming. It is not clear that the so-called dextrosapinic acid is in fact a new rosin acid. For example, the constants given for the acid,—melting point 145°C.; $[\alpha]_j = 40.5°$; $[\alpha]_v = 47°$ (43),—agree with those given by Brus and Levy (7) for a dihydroabietic acid, melting point 143–144°C., $[\alpha]_j = 41.8°$, $[\alpha]_v = 47°$, which they obtained by the hydrogenation of abietic acid over nickel. In this connection it should be mentioned that the presence of dihydroabietic acid in pine oleoresin has already been noted by Fleck and Palkin (20).

B. Pyroabietic acid

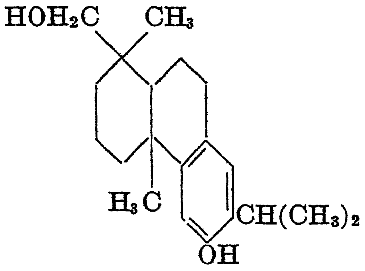
Levorotatory abietic acid can be slowly transformed to a dextrorotatory product by heat alone (57) or more rapidly by heat in combination with a catalyst such as palladium–charcoal (16, 17). On the basis of the empirical formula, $C_{20}H_{30}O_2$, this dextrorotatory material, originally named pyroabietic acid by Dupont and Dubourg (12), has been assumed to be the isomerization product of abietic acid. When, however, the absorption curves of this so-called pyroabietic acid and dehydroabietic acid, first prepared from abietic acid and identified by Fieser and Campbell (13), are superimposed, it becomes obvious that the two curves agree in shape and in the position of the maxima while differing only in intensity, the former acid showing a less intense band than that of dehydroabietic acid. The inference of this correspondence has been realized by Fleck and Palkin (18), who separated this pyroabietic acid into three components: dehydroabietic, dihydroabietic, and tetrahydroabietic acids. Rather than an isomerization this reaction is a disproportionation and dehydrogenation of abietic acid, the extent of either process depending on the temperature to which the abietic acid is heated. At 225°C. disproportionation is predominant, and the evolution of hydrogen is at a minimum; at higher temperatures (250–275°C.) the reaction is one of dehydrogenation, in which considerable hydrogen gas is evolved and dehydroabietic acid is the principal product. Confirmatory evidence has appeared (38, 50) establishing in a conclusive manner the nature of the reaction and the formation of dehydroabietic acid. Other methods of disproportionating abietic acid and pine rosin are also reported in which iodine (25), sulfur (39), and sulfur dioxide (33) are used as catalytic agents.

C. Dehydroabietic acid

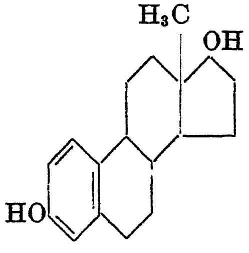
Dehydroabietic acid, $C_{20}H_{28}O_2$, is formed as described above by the dehydrogenation of abietic acid. It was, however, first prepared in a different way by Fieser and Campbell (13) under conditions which leave no doubt that the acid has structure XI, in which ring C of the abietic acid molecule is aromatic. These workers oxidized abietic acid in the cold with selenium dioxide and obtained the hydroxyabietic acid, XII. That the hydroxyl group is in position 6 seems certain, since XII does not lactonize on strong heating (eliminating positions 10 and 13) and gives isobutyric acid on permanganate oxidation (no hydroxylation of the isopropyl group). Since hydroxylation with selenium dioxide is presumed to occur on a methylene group adjacent to a double bond, position 6 is the only remaining location. The hydroxyabietic acid is dehydrated easily in boiling glacial acetic acid to give dehydroabietic acid in over 90 per cent yield.



XI XII



XIII



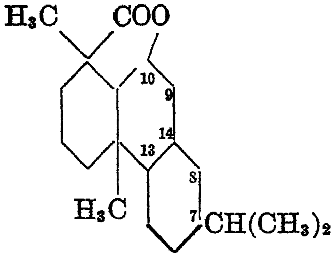
XIV

Dehydroabietic acid undergoes normal aromatic substitution reactions, such as nitration (13), sulfonation (14, 26), the Friedel–Crafts condensation (14), and halogenation (8). It is interesting to note that through use of substitution and reduction reactions 6-hydroxydehydroabietinol (XIII) has been prepared (15) to provide a structure analogous to that of estradiol (XIV). This derivative has definite estrogenic activity but shows some toxicity.

The first synthesis of the entire structure of the abietic acid molecule was achieved by Haworth and Barker (30) in 1939, who obtained the optically inactive structural analog of dehydroabietic acid. The synthetic compound, 1,12-dimethyl-7-isopropyloctahydrophenanthrene-1-carboxylic acid, has an absorption spectrum resembling that of dehydroabietic acid and gives retene on dehydrogenation. Resolution difficulties have prevented these authors from determining whether the synthetic acid is *dl*-dehydroabietic acid or a diastereoisomer.

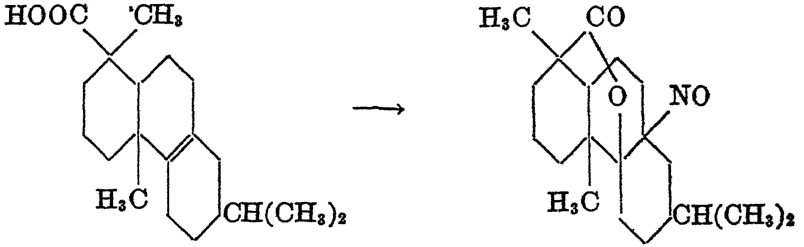
D. The dihydroabietic acids

Hydrogenation of abietic acid usually leads to mixtures of dihydro- and tetrahydroabietic acids whose separation and identification have proved difficult. A large number of dihydroabietic acids have been reported, with wide ranges of melting points and rotations. There is, however, agreement on one point: most dihydroabietic acids isolated yield a common lactone in the presence of cold mineral acids. Several authors (19, 26, 56) have reported the same lactone on treatment of different dihydroabietic acids with either cold hydrobromic acid or sulfuric acid and also the same hydroxytetrahydroabietic acid resulting from saponification of the lactone with alcoholic alkali. Hasselstrom and McPherson (28) have suggested that a γ-lactone (XV) is formed from a $\Delta^{9,10}$-dihydroabietic acid and that the corresponding hydroxytetrahydroabietic acid has its hydroxyl group at position 10. It would be more logical, however, to assume that saturation of one double bond of abietic acid would lead to a mixture of dihydro acids with the residual double bond at positions 9,14, 8,14, and 7,8. A further possibility, the 13,14-position, was considered by Fleck and Palkin (21) resulting from a bond shift under the influence of strong mineral acids from positions 9,14 and 8,14. This would allow the formation of a six-membered lactone ring (XVI) at position 13 rather than an improbable seven-membered lactone ring at position 14.

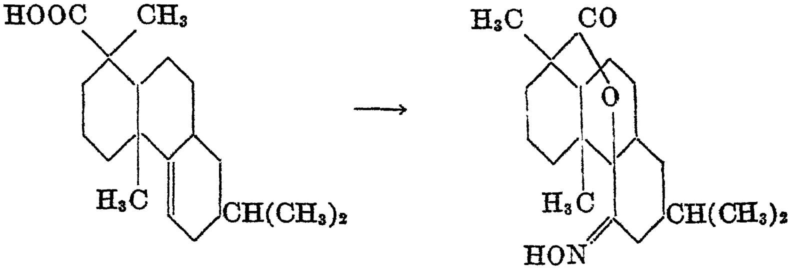


XV

These workers attempted to secure proof on this point by oxidizing the hydroxyl group of the hydroxytetrahydroabietic acid which is formed on opening the lactone ring. No ketone group was found which would result from the oxidation of a secondary hydroxyl group at position 9 or 10. However, this work is inconclusive because of the strong tendency of hydroxytetrahydroabietic acid and even its methyl ester to lactonize during the oxidation experiments. Support of position 13 as the point of lactonization has been given by Cox (11). Treatment of the lactone of dihydroabietic acid with methylmagnesium iodide results in the formation of two well-characterized dihydroabietic acids, one being levorotatory and the other dextrorotatory. Both acids reconvert easily to the original lactone in the presence of mineral acid. The levorotatory acid only yields a blue nitrosyl derivative (XVIII) with nitrosyl chloride, in agreement with structure XVII for this dihydroabietic acid. The dextrorotatory acid (XIX), whose structure is known with less certainty, gives with nitrosyl chloride a white compound characterized as an oximino lactone (XX).

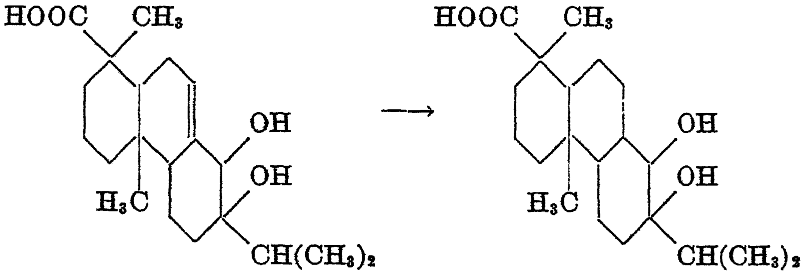


XVII XVIII



XIX XX

Ruzicka and St. Kaufmann (65) have attempted a characterization of a dihydroabietic acid obtained by hydrogenating abietic acid with a palladium–calcium



XXI XXII

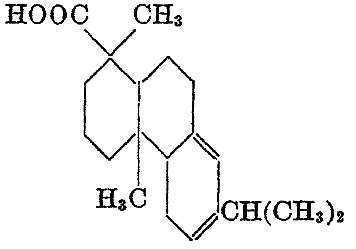
carbonate catalyst. They hoped to relate it to dihydroxyabietic acid (XXI) in which the positions of the hydroxyl groups are known (61), thereby determining the definite constitution of at least one dihydroabietic acid. Hydrogenation of XXI led to dihydroxydihydroabietic acid, a compound which served as the reference product with which to compare the oxidation product of their dihydroabietic acid. The two dihydroxydihydroabietic acids proved to be dissimilar, but this fact does not exclude the possibility of structure XXII for the dihydroxy derivative of their dihydroabietic acid, since it could be stereoisomeric with the reference compound, dihydroxydihydroabietic acid. Relatively little then is known of the hydrogenation products of abietic acid and further work is required to establish their constitution with certainty.

E. l-Sapietic acid

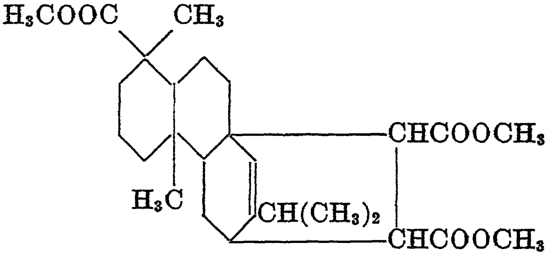
The name of this levorotatory acid, $C_{20}H_{30}O_2$, has been recommended for change by Hasselstrom and Bogert (24) from *l*-pimaric acid to *l*-sapietic acid in order to remove the erroneous implication of the former term. Early workers thought *l*-sapietic acid to be a stereoisomer of *d*-pimaric acid and therefore named it *l*-pimaric acid. It has since been found that the acid is in actuality a structural isomer and requires a new name.

There has been some question as to the number of double bonds in *l*-sapietic acid and furthermore as to the structural skeleton of this acid. That *l*-sapietic acid has only two double bonds is established by the hydrogenation studies of Ruzicka and Bacon (47), in which tetranitromethane (TNM) was used as a sensitive diagnostic reagent for the detection of relatively inert double bonds. Dihydro-*l*-sapietic acid, resulting from the addition of one mole of hydrogen to *l*-sapietic acid, gives an expected positive test with TNM (yellow coloration). On further hydrogenation of the dihydro acid with Adams' platinum catalyst in glacial acetic acid a mixture of isomeric tetrahydro-*l*-sapietic acids is obtained showing no coloration with TNM. Ruzicka and Bacon have precluded the possibility of isomerization during hydrogenation by recovering unchanged dihydro-*l*-sapietic acid from the action of glacial acetic acid alone. The presence of only two double bonds in the rosin acid is further evident from the fact that *l*-sapietic acid and dihydro-*l*-sapietic acid require two moles and one mole of oxygen, respectively, on titration with perbenzoic acid (37). The facile addition of maleic anhydride and of benzoquinone to these bonds leaves no doubt that these two double bonds are in conjugation in the same ring. The absorption maximum of *l*-sapietic acid at 272.5 μ (36) also demonstrates this latter conclusion, since abnormal conjugated dienes (the double bonds in one ring) absorb between 255 and 290 μ (73).

The dihydro- and tetrahydro-abietic acids are dehydrogenated by selenium to retene (about 70 per cent conversion). Similarly dihydro- and tetrahydro-*l*-sapietic acids are converted to retene by selenium in the same proportion, from which facts it can be stated with assurance that *l*-sapietic acid and abietic acid possess the same tricyclic skeleton, i.e., the hydrophenanthrene ring system. Ozonization of *l*-sapietic acid (48), as in the case of abietic acid, produces large amounts of isobutyric acid, a result which supports the placing of one of its double bonds adjacent to the isopropyl group, as in structure I. It follows also from this degradation product that the double bonds must be in ring C.

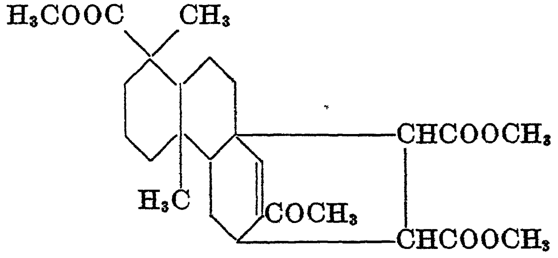


I

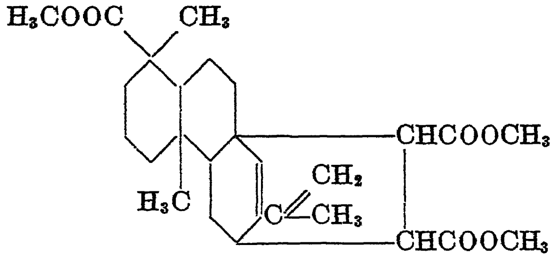


XXIII

Confirmatory support of structure I for *l*-sapietic acid can be given through the absorption spectrum of a degradation product obtained by Ruzicka and St. Kaufmann (64) from the adduct of maleic anhydride and *l*-sapietic acid. On ozonization of the trimethyl ester of this adduct, XXIII (based on the assumption of structure I for *l*-sapietic acid), two crystalline compounds are obtained in good yield, one being a singly unsaturated keto ester (XXIV), and the other a doubly unsaturated triester, for which structure XXV has been proposed by Ruzicka. Catalytic hydrogenation of XXV results in the absorption of one mole of hydrogen with regeneration of the starting material (XXIII), demonstrating that the double bond of the adduct has not shifted during ozonolysis. That the ozonization takes an abnormal course is clearly shown by the keto triester (XXIV). The action of an alkaline solution of sodium hypobromite on XXIV saponifies the two

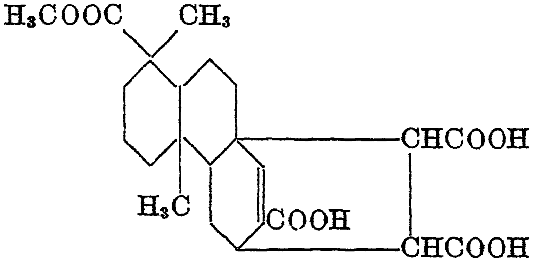


XXIV

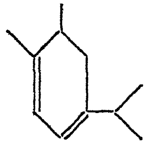


XXV

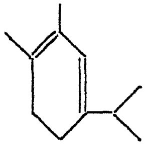
methyl ester groups of the maleic anhydride residue and gives the monomethyl ester of the tetracarboxylic acid, XXVI, with the production of bromoform. It is apparent, therefore, that hydroxylation has occurred at the tertiary carbon atom of the isopropyl group alpha to the double bond, followed by dehydration in the glacial acetic acid solvent and final oxidation of the isopropylidene group to the methyl ketone, XXIV. The $\lambda_{\text{max.}}$ (calculated) of this doubly substituted α,β-unsaturated ketone should be 239 $\mu \pm 5 \mu$, according to Woodward's data (72). The curve actually obtained for this compound shows a $\lambda_{\text{max.}}$ at 239 μ. The possibility of the double bond of the adduct being at the 6,7-position appears remote, since it would be difficult to explain the ready isomerization of *l*-sapietic acid having structure XXIX to abietic acid. Since structure I only can give an adduct with a double bond in the 7,8-position, structures XXVII, XXVIII, XXIX, XXX, and XXXI for ring C are ruled out, leaving structure I as the correct constitution of *l*-sapietic acid.



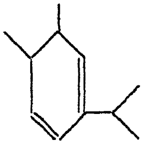
XXVI



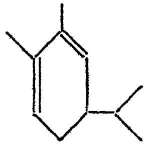
XXVII



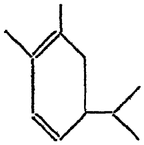
XXVIII



XXIX



XXX



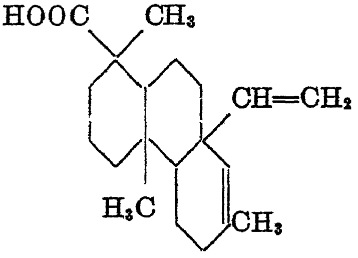
XXXI

Structure XXV of the doubly unsaturated triester, present also in the ozonolysis mixture, would appear to be in disagreement with the absorption maximum of this compound, since the conjugated diene system as shown by XXV requires a $\lambda_{\text{max.}}$ (calculated) at 232 $\mu \pm 5 \mu$ instead of the $\lambda_{\text{max.}}$ (observed) at 240 μ.

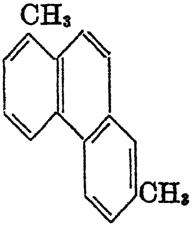
Independently Sandermann (66) and Arbusov (1) have arrived at the same conclusion regarding the correctness of structure I for *l*-sapietic acid on the basis of degradative work with the dimethyl acetylenedicarboxylate and α-naphthoquinone adducts of *l*-sapietic acid, respectively.

F. d-Pimaric acid

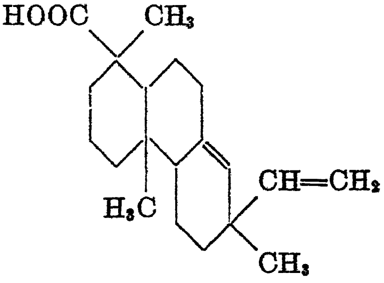
By 1932 the structure of *d*-pimaric acid, $C_{20}H_{30}O_2$, was known with respect to its carbon skeleton, the positions of the carboxyl group and the three methyl groups, and the presence of a vinyl group. There is left in question only the position of the vinyl group and that of the second double bond. Of the three positions, 9, 13, or 14, for the vinyl group, Ruzicka has chosen position 14, structure XXXII, since position 13 is not in accord with the isoprene rule and position 9 is contraindicated by the sole isolation of pimanthrene (XXXIII) on selenium dehydrogenation. That no 1-methyl-7-ethylphenanthrene, which should result from structure XXXIV on dehydrogenation, has been isolated, however, cannot be considered as evidence against XXXIV, since Barker and Clemo (3) have demonstrated that dehydrogenation of a *gem*-methylethyl group leads to the loss of the ethyl group. Further dehydrogenation work by Ruzicka and Sternbach (59) on derivatives of the methyl ester of dihydro-*d*-pimaric acid to 1,7,8-trimethylphenanthrene provides no evidence either for the position of the vinyl group or for the location of the second double bond which cannot be explained equally well by both structures XXXII and XXXIV. This work does show clearly that the second double bond is in either position 7,8 or 8,14, since the dibromide of methyl dihydro-*d*-pimarate (XXXVa or XXXVb), on treatment with methylmagnesium iodide followed by selenium dehydrogenation, gives 1,7,8-trimethylphenanthrene. Structure XXXIV for *d*-pimaric acid has received support from Hasselstrom and Hampton (27), who have been able to prepare a lactone of dihydro-*d*-pimaric acid under the same conditions used for the lactonization of the dihydroabietic acids. Strong saponification of the lactone likewise yields the hydroxytetrahydro-*d*-pimaric acid. According to structure XXXII lactonization would have to occur at the vinyl group, resulting in an improbable eight- or nine-membered lactone ring. The postulated double-bond shift in the case of the dihydroabietic acids could take place, however, in structure XXXIV (but not in structure XXXII) with the point of lactonization at position 13. The similar sta-



XXXII

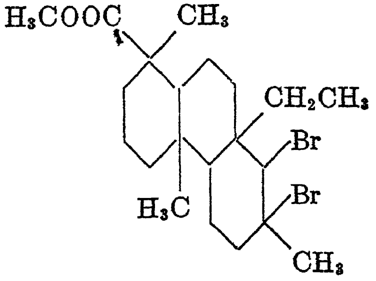


XXXIII

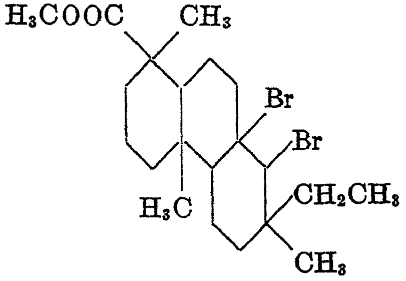


XXXIV

bilities of the lactones of both dihydroabietic and dihydro-*d*-pimaric acids indicate the same point of lactonization. Of further interest is the isolation of a hydroxylactone by Fleck and Palkin (22) from dihydro-*d*-pimaric acid by working at low temperatures (−20° to −30°C.) in sulfuric acid. This hydroxylactone shows an active hydrogen atom (Zerewitinoff) and the indicated hydroxyl group cannot be acetylated. It is inferred from this that the hydroxyl group is situated at the tertiary C_{14} position, analogous to the nitroso group in the nitrosyllactone, XVIII.



XXXVa

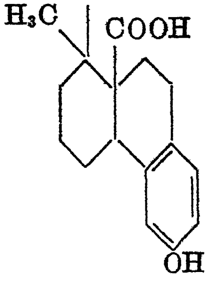


XXXVb

Proof of structure XXXIV for *d*-pimaric acid has been reported by Harris (23) from the degradation of the acid to a 1,5-dialkylated naphthalene derivative. The details of this work have not yet been published and therefore cannot be evaluated.

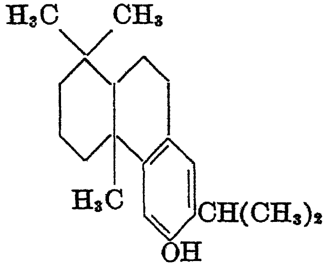
G. Podocarpic acid

The constitution of podocarpic acid, $C_{17}H_{22}O_3$, first isolated by Oudemans in 1873 from the resin of the Javanese tree *Podocarpus cupressinus*, has been completely established. That podocarpic acid has a tricyclic nucleus was shown by Sherwood and Short (67) from the isolation of 1-methylphenanthrene on selenium dehydrogenation of podocarpic acid and from the phenol, 6-hydroxy-1-methylphenanthrene, resulting from sulfur dehydrogenation. The presence of a hydroxyl group of phenolic character in this resin acid, coupled with the evidence for the presence of an aromatic ring in the nucleus, shows podocarpic acid to be a new type of resin acid not previously encountered. With these facts structure XXXVI has been postulated for podocarpic acid with the carboxyl group at position 11 on the basis of the greater resistance of its carboxyl group to esterification and saponification than the carboxyl group of dehydroabietic acid.

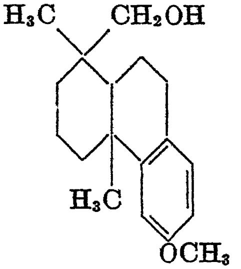


XXXVI

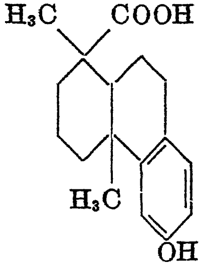
The opinion has been advanced that podocarpic acid differs from 6-hydroxydehydroabietic acid only in not having a C_7 isopropyl group (15). This explanation is, however, an oversimplification, since Campbell and Todd (9) have found that 7-isopropylpodocarpic acid is not identical with the dehydroabietic acid derivative. If it is presumed that these two acids differ further in configuration at the C_1-position, the dissimilarity above is explained and also the difference in the degree of hindrance of the carboxyl group as compared to that of dehydroabietic acid. Campbell and Todd (10) tested this point by eliminating the center of asymmetry at the C_1-position of both 7-isopropylpodocarpic acid and 6-hydroxydehydroabietic acid: reduction of the carboxyl groups to methyl groups through the acid chlorides and aldehydes giving on the one hand 7-isopropylpodocarpane and on the other 6-hydroxydehydroabietane. These compounds are indeed identical and even further, somewhat fortuitously, correspond to the resin alcohol, ferruginol, isolated shortly before this work by Brandt and Neubauer (5). By reference to the proved structure of dehydroabietic acid the structures of 7-isopropylpodocarpane, 6-hydroxydehydroabietane, and ferruginol are conclusively established as XXXVII. There remain then two possibilities, positions 1 and 12, for the attachment of the carboxyl group of podocarpic acid, since position 11, as in structure XXXVI, is eliminated by the establishment of structure XXXVII. The transformation of methyl *O*-methylpodocarpate to 1-ethyl-6-methoxyphenanthrene (10) effectively proves the constitution of podocarpic acid as represented by XXXIX, in which the carboxyl group is at position 1. This conversion was carried out by reducing the methoxy ester to the corresponding podocarpinol (XXXVIII), followed by a Wagner–Meerwein rearrangement of this primary alcohol and dehydrogenation.



XXXVII



XXXVIII

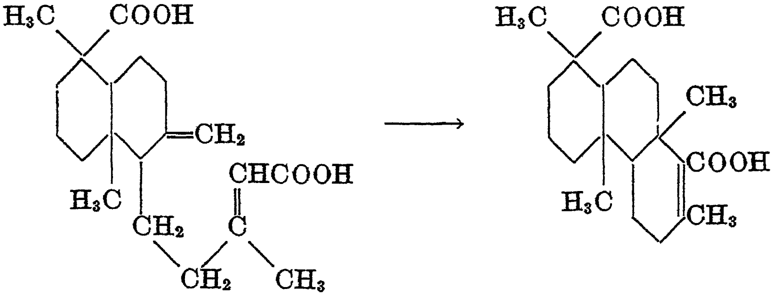


XXXIX

The podocarpic acid structure has since been synthesized by Bhattacharyya (4) and Haworth and Moore (31), but again, as in the case of the synthesis of the structural analog of dehydroabietic acid, the difficulty encountered in the resolution of the resulting product has so far prevented the isolation of the isomer identical with the natural acid.

H. Agathic acid

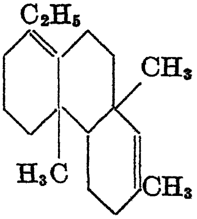
Agathic acid or agathicdicarboxylic acid, $C_{20}H_{30}O_4$, is found in those fossil resins known as the Manila and kauri copals. Much of the early work on the constitution has been done by Ruzicka and Hosking, leading to the proposed structure XL. Agathic acid isomerizes on warming with formic acid to two isomeric isoagathic acids whose tricyclic structure (XLI) has been demonstrated by conversion to 1,7-dimethylphenanthrene. The isoagathic acids differ presumably in the position of the double bond in ring C. As in the case of abietic acid, there is a strong element of uncertainty regarding the homogeneity of a sample of agathic acid. The impurity in this acid would probably be an isomeric acid or acids in which the exocyclic double bond is in the ring. Therefore the constitution of agathic acid can be based only on the acid predominant in the material used.



XL

XLI

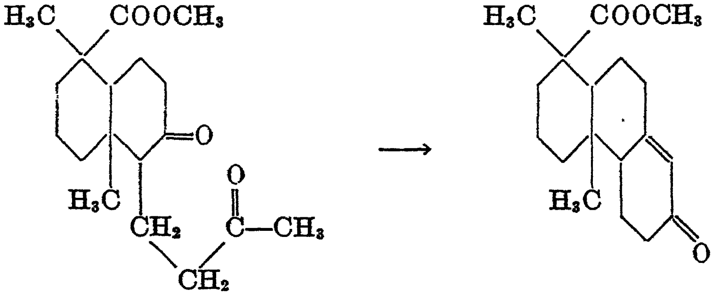
The carboxyl groups at position 8 of both agathic and isoagathic acids are easily eliminated, in conformity with structures XL and XLI, to give the nor acids. The extreme difficulty of esterification and saponification of the second carboxyl group relates its configuration to that of podocarpic acid. The location of this inert carboxyl group has been determined by Ruzicka and Jacobs (55), who first decarboxylated one of the isoagathic acids to isonoragathic acid and then reduced the remaining carboxyl group to the corresponding primary alcohol. On dehydration a Wagner–Meerwein rearrangement takes place to give structure XLII.

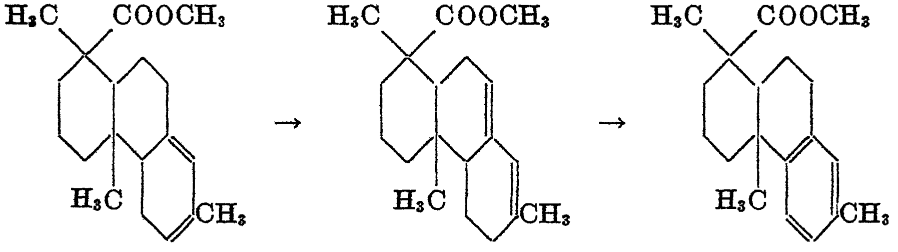


XLII

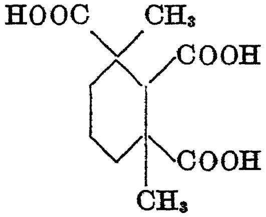
Dehydrogenation of XLII gives 1-ethyl-7-methylphenanthrene, thus establishing the attachment of the hindered carboxyl group at C_1.

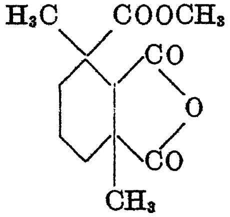
The ozonolysis of the dimethyl ester of agathic acid itself places the two double bonds in agathic acid with certainty. From this degradation Ruzicka, Bernold, and Tallichet (52) have isolated formaldehyde originating from the cleavage of the exocyclic methylene group, oxalic acid from the fission of the double bond at position 7,8, and the diketo ester (XLIII). In basic solution the diketo ester undergoes cyclization to the tricyclic keto ester (XLIV). This α,β-unsaturated ketone has a $\lambda_{max.}$ at 238 μ in agreement with the expected $\lambda_{max.}$ (calculated) of 239 μ ± 5 μ (72). Treatment of XLIV with methylmagnesium iodide, followed by dehydration, results in the diene ester (XLVb), having a $\lambda_{max.}$ at 238 μ ($\lambda_{max.}$ of abietic acid is 237.5 μ). The shift of the double bonds in XLVa to XLVb is the same one occurring in the isomerization of *l*-sapietic acid to abietic acid. Further analogy is found by the partial dehydrogenation of XLVb with palladium-charcoal to the aromatic structure XLVI, as in the disproportionation of abietic acid to dehydroabietic acid. Selenium dehydrogenation of XLVb yields the hydrocarbon, pimanthrene.


XLIII XLIV


XLVa XLVb XLVI

Although by comparison with the other resin acids the third methyl group for agathic acid can be presumed to be at the bridgehead of rings A and B, position 12, the argument is inconclusive. Among the products originating from the permanganate oxidation of abietic acid (53), there is isolated the optically inactive tricarboxylic acid, XLVII (internally compensated), to which Ruzicka and Bernold (51) have attempted to relate a degradation product of agathic acid. On


XLVII


XLVIII

similar oxidation with permanganate the dimethyl ester of agathic acid gives an anhydride of the monomethyl ester of a tricarboxylic acid, presumably of structure XLVIII. This ester resists complete saponification and shows positive rotation, in contrast to the optical inactivity of the anhydride of XLVII. It is therefore reasonable to suspect that the anhydride of XLVII (from abietic acid) and XLVIII differ only in configuration at C_1. Structure XL can therefore be considered as very probable for agathic acid.

I. Miropinic and isomiropinic acids

Brandt and Neubauer (6) isolated in 1940 two isomeric acids, $C_{20}H_{30}O_2$, from the miro resin of a New Zealand pine, *Podocarpus ferrugineus*, which show a structural similarity to *d*-pimaric acid in that miropinic acid gives pimanthrene on selenium dehydrogenation. Isomiropinic acid probably has the same tricyclic structure, since it can be formed by isomerization of miropinic acid in methyl alcohol containing hydrogen chloride. Miropinic acid gives two unsaturated dihydro acids on catalytic hydrogenation, which in turn further absorb hydrogen to give two different saturated tetrahydro acids and a third dihydro acid. The constitution of these two resin acids awaits further clarification.

J. Vouacapenic acid

A relatively little known resin acid, vouacapenic acid, $C_{20}H_{28}O_3$, was isolated in 1930 by Spoelstra (68) from the heartwood of *Vouacapoua americana*, a tree indigenous to South America, in the form of its methyl ester. The difficulty in the saponification of this ester is reminiscent of the structurally hindered carboxyl groups of podocarpic acid and agathic acid. The acid has no free hydroxyl group and it appears further that the third oxygen atom is bound in a bridge. From perbenzoic acid oxidation and catalytic hydrogenation data it is probable that vouacapenic acid has two double bonds, complete hydrogenation giving a tetrahydro derivative. Further hydrogenation results in a hexahydro compound containing a hydroxyl group having active hydrogen (Zerewitinoff method), presumably arising from the opening of the oxygen bridge. Further work is in progress regarding the structural elucidation of this interesting resin acid (70).

K. Cativic acid

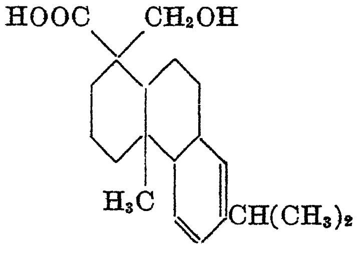
Cativic acid, $C_{20}H_{34}O_2$, which was reported and named by Kalman (32), is obtained in about 95 per cent yield from the gum of the "Cativa" tree, *Prioria capaifera*, indigenous to the Caribbean area of Central America. Cativic acid is obtained as a clear, viscous liquid of cyclic constitution, but differs from the resin acids as a group in that it is very readily esterified, a fact which suggests the presence of a primary carboxylic acid group. At least one double bond appears probable in the molecule, since oxidation with alkaline permanganate gives a crystalline dihydroxy derivative. No further work has been reported on this acid and its structure remains obscure.

L. Rubeabietic and rubenic acids

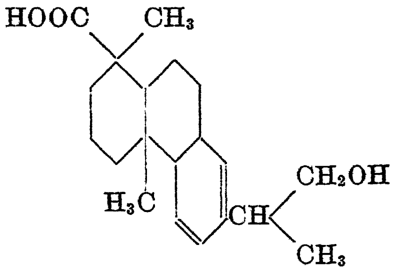
Two resin acids have been isolated by Kono and Maruyama (34, 35) from the resin of *Ceroplastes rubens* Mask. of Japan, to which the names rubeabietic acid

($C_{20}H_{30}O_2$) and rubenic acid ($C_{20}H_{30}O_3$) have been assigned. Rubeabietic acid, on reduction of its methyl ester, gives the corresponding resin alcohol, whose acetate, benzoate, and phenylurethan were identified with those same derivatives of abietic acid. On oxidative degradation of rubeabietic acid a C_{11} tricarboxylic acid is obtained as in the case of abietic acid. The dextrorotatory nature of this resin acid suggests that it may be a *d*-isomer of abietic acid.

The optically inactive rubenic acid is presumed to have two double bonds, since it can be catalytically hydrogenated over platinum black to the tetrahydro derivative. The presence of hydroxyl group in the molecule is indicated by the selenium dehydrogenation of rubenic acid to hydroxyretene as well as retene itself. Furthermore, the reduction of its methyl ester with sodium and alcohol yields a dihydroxy compound. This is the first example of a hydroxyabietic acid occurring in nature. Kono and Maruyama have proposed the following structures for rubenic acid:

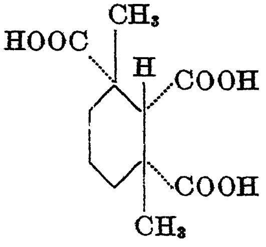


or

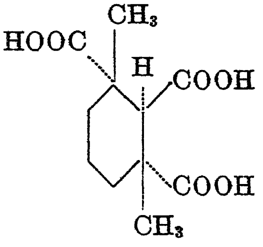


IV. CONFIGURATION

A discussion of the configurations of the resin acids is necessarily based on the C_{11} acid isolated by Ruzicka and coworkers (53) from the permanganate oxidation of abietic acid. The optical inactivity of this acid permits the conclusion that its constitution must be represented by either of the two *meso* structures, XLIXa or XLIXb. The possibility that inversion at C_{11} occurred during the oxidation is excluded by the fact that an optically active acid has been formed from agathic acid.

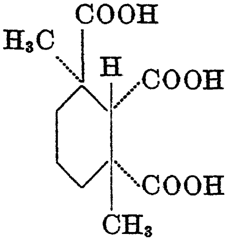


XLIXa

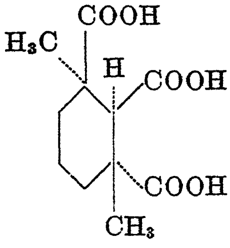


XLIXb

Inasmuch as abietic acid has been converted to dehydroabietic acid under conditions which permit no change in configuration at rings A and B, it is certain that rings A and B of dehydroabietic acid possess either structure XLIXa or

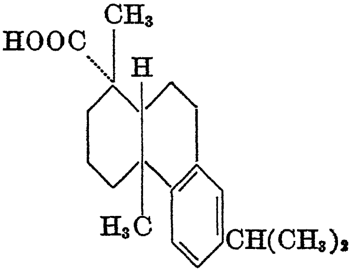


La

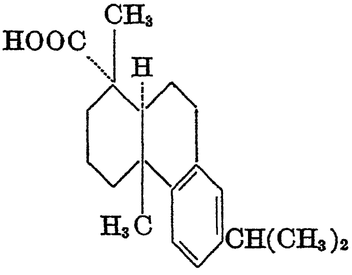


Lb

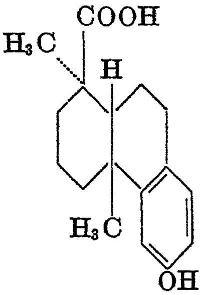
XLIXb. It has already been shown by Campbell and Todd (10) that 6-hydroxydehydroabietic acid differs only from podocarpic acid in having an isopropyl group at C_7 and a different configuration at C_1. Rings A and B of podocarpic acid must therefore have structure La if rings A and B of dehydroabietic acid are *cis* as in structure XLIXa, or structure Lb if formula XLIXb, in which rings A and B are *trans*, is correct for dehydroabietic acid. Using Stewart models Campbell has made the point that the much greater resistance of the carboxyl group of podocarpic acid to esterification and saponification allows a choice to be made. According to structures LIa and LIIa, in which the rings are *cis*, the carboxyl group of LIa is much more hindered than that of LIIa, a conclusion which is contrary to the facts. In structures LIb and LIIb the hindrance relationship is reversed, and it is therefore probable that dehydroabietic acid has structure LIb and podocarpic acid has structure LIIb. Support for this designation of configuration has been obtained by Zeiss (74) in which the tertiary diphenyl carbinol of dehydro-



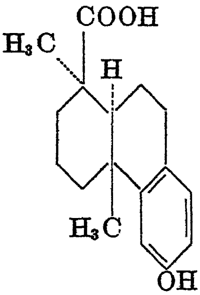
LIa



LIb

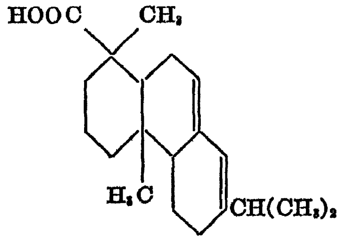
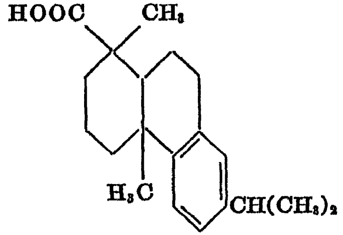
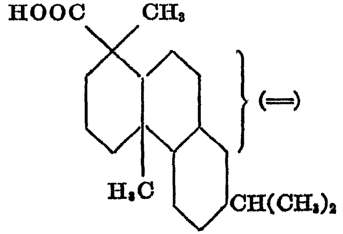


LIIa



LIIb

Physical properties

RESIN ACID	MELTING POINT	$[\alpha]_D$	METHYL ESTER		REFERENCES
			Melting point	$[\alpha]_D$	
*	°C.		°C.		
Abietic acid  	161–165	−80°			(69)
	170–174	−104°			(45)
	174–175	−115.6°			(2)
Dehydroabietic acid  	173–173.5	+62°	62–63	+60°	(14)
Dihydroabietic acid  	193–194	+9°			(49)
	174–176	+108°			(19)
	217.5–218.5	−23°	131.5–132.5	−21.5°	(29)
	166	−26°			(41)
	177	+125°			(41)
	185–186	−36°			(11)
	147–148	+68°			(11)

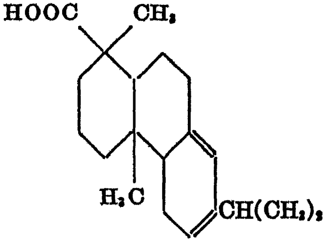
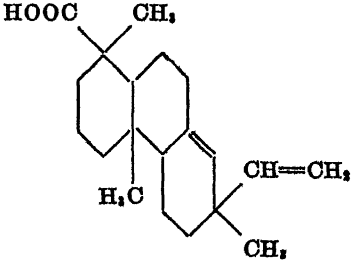
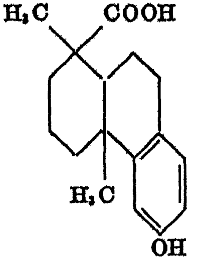
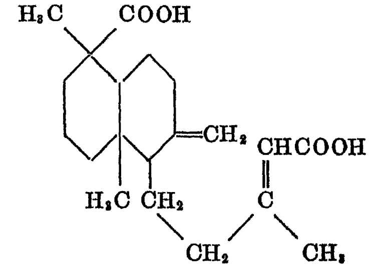
l-Sapietic acid 	148–151	−282°	63–64	−268°	(47)
d-Pimaric acid 	218–219	+75°			(22)
Podocarpic acid 	193	+144°	208		(67)

TABLE 1—*Concluded*

RESIN ACID	MELTING POINT	$[\alpha]_D$	METHYL ESTER		REFERENCES
			Melting point	$[\alpha]_D$	
	°C.		°C.		
Agathic acid	203–204	+56.1°			(54)
					
Miropinic acid	160	−3.6°			(6)
Isomiropinic acid	284	+21.2°			(6)
Vouacapenic acid	226–229	+107–108°	105	+101°	(68)
Cativic acid	194–195/1 mm.*				(32)
Rubeabietic acid	161–162	Dextrorotatory			(35)
Rubenic acid	88	Optically inactive			(34)

* Boiling point.

abietic acid has been prepared. Structure LIb admits the possibility of this carbinol for dehydroabietic acid, while structure LIIb for podocarpic acid does not. In accord with the failure of prior attempts by Sherwood and Short (67) to obtain the diphenyl carbinol of podocarpic acid, the latter prediction holds true. There remains, however, the disturbing fact that structure XLIXa accounts readily for the ease of lactonization of hydroxytetrahydroabietic acid in that the carboxyl group of the hydroxy acid is then near the C_{13}-position. The point of lactonization at C_{13} is not a closed problem, and more conclusive evidence regarding the resin acid configurations requires reference to the *cis*- and *trans*-decalin series.

A. *The cis acids*

Without any further evidence regarding the *cis* or *trans* positions of rings A and B, the resin acids may be classified into two groups depending on the reactivity of their C_1 carboxyl groups. The *cis* group comprises those acids whose C_1 carboxyl group is *cis* with respect to the C_{12} methyl group. Podocarpic acid is relegated to this group on the basis of the discussion above. Not only the inertness of the C_1 carboxyl group but also the optical activity of its C_{11} acid obtained by degradative oxidation places agathic acid in this classification. Although little is known of the constitution of vouacapenic acid, the behavior of its acid group relates it in this connection to the other strongly hindered acids.

B. *The trans acids*

Most of the resin acids known are of the type in which the C_1 carboxyl group is *trans* with respect to the C_{12} methyl group. These include abietic acid, *l*-sapietic acid, dehydroabietic acid, the dihydroabietic acids, and *d*-pimaric acid. Solely on the basis of the relative ease of esterification miropinic and isomiropinic acids may be tentatively added to this series. Cativic acid is esterified with great ease and very probably belongs to neither class. Rubeabietic and rubenic acids appear to be molecules of the abietic type and may be regarded, therefore, as *trans* acids.

V. PHYSICAL PROPERTIES

Table 1 presents a summary of the physical properties of the resin acids.

The author wishes to express his indebtedness to Professor W. von E. Doering of Columbia University and to Professor David Todd of Amherst College for their helpful suggestions and criticisms during the preparation of the manuscript. He is also grateful to Dr. E. E. Fleck and Dr. T. Hasselstrom, who have generously supplied reprints of their papers, and to Mr. S. E. Brown and Mrs. B. D. Zeiss for their assistance in the proofreading of this paper.

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THE PREPARTION OF NITRILES

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I. INTRODUCTION

A. HISTORICAL BACKGROUND

Hydrogen cyanide was first prepared in 1782 by Scheele (511), who was later killed while attempting to isolate the anhydrous material. In 1811 Gay-Lussac (213) succeeded in preparing the pure acid and established its constitution. The first syntheses of nitriles were reported by Wöhler and Liebig, who prepared benzoyl cyanide and benzonitrile in 1832 (609), and by Pelouze who obtained propionitrile in 1834 (455).

Nearly a century followed before the volume of research in nitrile chemistry reached sizable proportions. It is true that many significant contributions to this field were made during this interval, but investigators were probably understandably reluctant to devote major efforts to such researches because of the hazards of toxicity. A more significant factor may have been the availability and price of the inorganic cyanide raw materials. The latter deterrent was effectively removed by increased attention to the nitrogen fixation problem during the first World War.

As a result, the fifteen-year period from 1920 to 1935 showed a fourfold increase in the average number of annual papers on nitrile chemistry. Subsequently, research in this field has continued at an ever-increasing tempo. The past decade, moreover, has witnessed the transition of organic nitriles from a position of laboratory curiosities to that of large-tonnage chemicals of commerce. Of the score or more that have become commercially available in the past ten years one might cite acrylonitrile (plastics, synthetic rubber, synthetic fibers), phthalonitrile (dyestuffs), adiponitrile (synthetic fibers), acetone cyanohydrin (plastics), or trichloroacetonitrile (fumigant) as examples of compounds which have reached large-volume production. Numerous others have found application in the fields of synthetic resins, war gases, insecticides, specialty solvents, and especially as intermediates for the chemical synthesis of pharmaceuticals, dyestuffs, vitamins, and plastics.

B. NATURAL OCCURRENCE

Nitriles do not occur in high concentration in nature, but their presence has been detected in minor amounts in a large number of plants. They are most commonly present as various glycosides of mandelonitrile, although glycosides of the cyanohydrins of other aldehydes and ketones (such as acetone) have been reported. Amygdalin, which is hydrolyzed to gentiobiose and *d*-mandelonitrile, is probably the best known example of this type. Concentrations of hydrogen cyanide run as high as 1 per cent of the dry weight of *Pangium edule* leaves. Rosenthaler states that lesser amounts are found in the stem, roots, flowers, leaves, fruit, and seeds of 360 varieties of 150 species of 41 cyanogenetic plant families of trees, flowers, ferns, legumes, mushrooms, etc. (495). They are generally not found in plants containing alkaloids or terpenes. The biochemical formation of the cyanophoric glycosides may be partially explained by Parrod's demonstration (451) that certain reducing sugars can be oxidized in the presence of ammonia and atmospheric oxygen to urea and hydrogen cyanide.

Phenylacetonitrile and β-phenylpropionitrile have been isolated from certain essential oils (272, 501), while acetonitrile has been isolated from coal tar and gas tar (575). Propionitrile, butyronitrile, valeronitrile, and some higher homologues have been identified as components of bone oil (588).

Because of the low concentrations involved, the extraction of nitriles from natural sources does not constitute a convenient method of preparation.

C. SCOPE OF REVIEW

The present survey is limited to a discussion of the esters of hydrogen cyanide. Other derivatives of cyanogen, such as the cyanates, isocyanides, thiocyanates, and cyanamides, are beyond the scope of this review. Hydrogen cyanide itself and the cyanogen halides will be considered only insofar as they enter into or illustrate the synthesis of the higher nitriles.

First to be discussed are the methods of synthesis in which the cyano group is introduced directly into an organic compound, with the formation of a new carbon skeleton. Consideration will then be given to indirect methods in which the nitrogen is introduced and the carbon–nitrogen triple bond is formed. Finally, a very abbreviated statement dealing with the toxicity of the nitriles is presented, since these properties should be considered by those engaging in preparative work. A monograph has recently appeared which gives an extensive review of the chemical reactions of organic cyanogen compounds (402a).

D. NOMENCLATURE

Fehling is credited with coining the term "nitrile" in 1844 (12a). At least eight systems of nomenclature for these compounds have been employed. These are illustrated by the following names for $CH_3CH_2CH_2CN$: (*a*) butyronitrile, (*b*) propyl cyanide, (*c*) cyanopropane, (*d*) propanenitrile, (*e*) butanenitrile, (*f*) butanonitrile, (*g*) propane carbonitrile, and (*h*) nitrilobutane. System d, in which the term "nitrile" was considered as a replacement of a hydrogen atom, was used for certain structures by *Chemical Abstracts* before 1936. This has been abandoned in favor of system e, in which "nitrile" is considered to be replacing a methyl group, and system g, in which "carbonitrile" replaces a carboxylic acid substituent. These usages conform to the recommendations of the Geneva Congress of 1892 (Rule 39) and of the International Union of Chemistry at Liége in 1930 (Rule 32). The prefix "nitrilo" (system h) refers to the $N\equiv$ radical and is seldom encountered. Modern usage favors the nomenclature derived from the common name (system a) rather than the Geneva name (system f) of the analogous acid. Where necessary in a polyfunctional compound, the prefix cyano (system c) is used. The once popular system (system b) of naming nitriles as esters of hydrocyanic acid is being slowly abandoned.

II. Preparation by Metathesis (Alkylation of Cyanides)

The simple metathetical reaction involving direct esterification of an alcohol with hydrocyanic acid has only recently been demonstrated with certainty. Such reactions had been reported to take place in the vapor phase over dehydration catalysts such as alumina or thoria at about 300°C. (433). However, the actual reagent in these cases may have been either the olefin or the ether derived from the alcohol. Both of these derivatives are known to react with hydrogen cyanide (see pages 222, 244). Recent reports from Germany indicate that 2-butene-1,4-diol will react with hydrogen cyanide in the liquid phase at 60–80°C. The catalyst consists of ammoniacal cuprous chloride dissolved in dilute hydrochloric acid.

$$HOCH_2CH{=}CHCH_2OH + 2HCN \xrightarrow[\text{(70 per cent yield)}]{Cu_2Cl_2\cdot NH_4Cl} CNCH_2CH{=}CHCH_2CN + 2H_2O$$

Other reactive alcohols, such as allyl alcohol and benzyl alcohol, react similarly (530a). However, the principal methods of esterification have all been indirect ones, usually involving the reaction of a mineral acid ester of the alcohol with a salt of hydrocyanic acid.

A. ALKYL SULFATES AND METAL CYANIDES (PELOUZE SYNTHESIS)

Propionitrile, the first aliphatic nitrile to be described in the literature, was prepared by Pelouze in 1834 by the reaction of potassium ethyl sulfate and potassium cyanide (455). Ethyl sulfate gives similar results (583).

$$(\mathrm{C_2H_5})_2\mathrm{SO_4} + \mathrm{KCN} \rightarrow \mathrm{C_2H_5CN} + \mathrm{C_2H_5OSO_3K}$$

Although the reaction was extended to the preparation of phenylacetonitrile (30), its chief application seems to have been the preparation of the lower aliphatic nitriles. It still is one of the most convenient laboratory methods for the preparation of acetonitrile and propionitrile. Methyl sulfate reacts at room temperature, while ethyl sulfate requires external heating. Yields calculated on the basis of the above equation are reported to be quantitative. This is not strictly true, since alkyl (methyl to isoamyl) potassium sulfates have been shown to react at somewhat higher temperatures with a second mole of potassium cyanide in 15–90 per cent yields (19, 580).

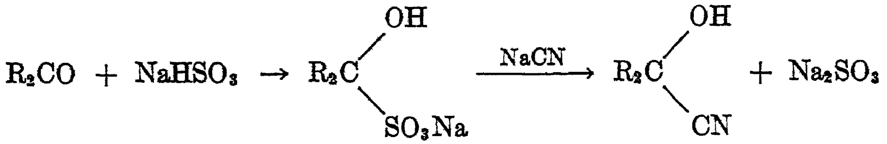
$$\mathrm{ROSO_3K} + \mathrm{KCN} \rightarrow \mathrm{RCN} + \mathrm{K_2SO_4}$$

By selection of a suitable temperature cycle the utilization of both alkyl groups may be effected in high yield (583).

The nitrile may be contaminated with as much as 10 per cent of the isocyanide, a result which seems to be caused partly by the presence of water. Sodium cyanide is stated to cause more hydrolysis of the nitrile group than potassium cyanide. This may be avoided by the use of an non-aqueous diluent such as xylene or tetralin which boils at a temperature greater than 130°C. (470).

Alkyl arylsulfonates react similarly with equimolar quantities of potassium cyanide to give aliphatic nitriles (191). The methyl ester is converted in higher yield than the ethyl ester (489). However, high yields are again obtained in the case of the higher aliphatic esters, and cetyl *p*-tolylsulfonate is converted to margaric nitrile in 86 per cent yield (524). Alkyl esters of methanesulfonic acid in some cases give better yields of alkyl cyanides than are obtained from the esters of *p*-toluenesulfonic acid (622). However, the secondary butyl ester gave largely 2-butene instead of α-methylbutyronitrile.

The bisulfite modification in the preparation of cyanohydrins of aldehydes and ketones is a special case in which a sodium sulfonate group is smoothly replaced by the cyanide ion (see page 231).



$$\mathrm{R_2CO} + \mathrm{NaHSO_3} \rightarrow \mathrm{R_2C}\begin{matrix}\diagup\mathrm{OH}\\ \diagdown\mathrm{SO_3Na}\end{matrix} \xrightarrow{\mathrm{NaCN}} \mathrm{R_2C}\begin{matrix}\diagup\mathrm{OH}\\ \diagdown\mathrm{CN}\end{matrix} + \mathrm{Na_2SO_3}$$

The use of phosphoric acid esters instead of the sulfates has apparently received scant attention. Williamson described the reaction of aryl phosphates with potassium cyanide in 1854 (601). This synthesis of aromatic nitriles, which gives 15–20 per cent yields, was extended by Heim (254) and Kreysler (331). Triethyl phosphate is stated to give propionitrile when heated with sodium cyanide (470).

B. ARYL SULFONATES AND METAL CYANIDES

The classic synthesis of benzonitrile by the fusion of the alkali metal salts of benzenesulfonic acid with potassium cyanide was discovered by Merz in 1868 (393). Further study of the reaction (394) revealed that a good yield of β-naphthonitrile was obtained from sodium β-naphthalenesulfonate by treatment with an excess of sodium cyanide. Naphthalene, water, hydrogen sulfide, ammonium carbonate, and ammonium cyanide were identified among the by-products. Increasing the mole ratio of sodium cyanide to sulfonate above 2:1 does not better the yield. The potassium salts give slightly better yields, while the calcium salts are inferior. α-Naphthonitrile is obtained in 50 per cent yield by the action of sodium cyanide (593).

Witt showed that the less toxic potassium ferrocyanide gave somewhat better results (606). In general, the yields of purified aromatic nitriles vary from traces to 60 to 80 per cent depending on the structure of the reacting compound. Dry reagents, intimate mixing, and uniform heating of the reaction mass to high temperatures appear desirable. The use of about 70 per cent sand in the reaction mixture is claimed to increase yields by modifying the exothermic reaction (248), while the introduction of a quantity of iron filings is recommended to aid the distribution of heat (581). A smoother reaction and increased yields are also obtained by heating the reagents in an inert diluent such as a mineral oil having a boiling range of 310–400°C. (467). The reaction is commonly effected under vacuum or in the presence of a stream of inert gas, such as carbon dioxide, to facilitate the rapid removal of product from the reaction zone.

A number of dicyano derivatives of benzene, biphenyl, naphthalene, and higher condensed-ring systems have been prepared from the corresponding disulfonates. Yields are usually low (less than 20 per cent) and the product is contaminated with mononitrile. Phthalonitriles and naphthalonitriles have also been obtained from halobenzene- or halonaphthalene-sulfonic acids (144, 398, 436). Sodium 1,3,5-benzenetrisulfonate when fused with potassium cyanide is reported to give a small yield of trimesonitrile (288).

Whereas only traces of isophthalonitrile are obtained by this method (398), terephthalonitrile is obtained in yields of about 20 per cent (436). These observations suggest an activation of the sulfonic acid or halogen group by the cyano group if the two radicals are separated by an even number of carbon atoms. This tendency has been confirmed by Bradbrook and Linstead, who undertook the synthesis of ten different dicyanonaphthalenes by fusion of the appropriate sodium cyanonaphthalenesulfonate with potassium ferrocyanide (64). Thus, under comparable conditions, 1-naphthonitrile-2-sulfonate, -4-sulfonate, -5-sulfonate, and -7-sulfonate were converted to the naphthalonitriles in 31–75 per cent yields, while the corresponding 3-sulfonate, 6-sulfonate, and 8-sulfonate gave yields of only 9–18 per cent. Confirmatory results were obtained with the 2-naphthonitrile derivatives, the 1-sulfonate and 6-sulfonate being converted in 84 and 42 per cent yields, respectively, while the 7-sulfonate gave only 8 per cent of the corresponding dinitrile. The effect is especially pronounced when the cyano group is in the same ring as the sulfonic acid group. This interesting activation is apparently not entirely explainable by the principles of resonance or vinology, since an analogous situation is found in the aliphatic series where no aromatic nuclei or double bonds exist (see page 197). A further conclusion is that there is no appreciable difference in yields or ease of reaction between α- or β-positions of the naphthalene ring.

Substituents such as alkyl, amino, or keto groups (336) appear to be unchanged by fusion with the alkali cyanide or ferrocyanide reagent. The reaction is successful with sulfonates of heterocyclic amines such as quinoline and pyridine. Sodium pyridine-3-sulfonate has been converted to nicotinonitrile in 46 per cent yield by this method (374), which forms the basis of a commercial synthesis of nicotinic acid and its amide (467). α-Cyanothiophene may also be prepared by means of this synthesis (160).

Certain unexpected side-reactions have been reported. Thus, potassium acenaphthene-3-sulfonate and potassium ferrocyanide give acenaphthylene as the main product (443). King and Wright have shown that migrations of the nitrile group from the β- to the α-position of the naphthalene nucleus sometimes occur in this synthesis (311). When sodium 2-naphthonitrile-7-sulfonate or the 2,7-naphthalenedisulfonate is treated with potassium cyanide, some 1,7-dicyanonaphthalene is obtained together with the 2,7-derivative. Similarly, 2-naphthonitrile-6-sulfonate gives a certain amount of 2,5-dicyanonaphthalene, together with the expected product.

The reaction of arylsulfonic acid salts with metal cyanides has been discussed at some length by Suter (553a).

C. HALIDES AND METAL CYANIDES

1. *Aliphatic halides*

The reaction of an organic halide and a metallic cyanide was first investigated in 1832 by Wöhler and Liebig (609), who obtained benzoyl cyanide by distillation of benzoyl chloride over mercuric cyanide. Conversion of alkyl halides to the nitriles by the use of the cyanides of alkali metals was accomplished by Williamson in 1854 (600) and the action of the heavy metal cyanides was studied by Gautier (209).

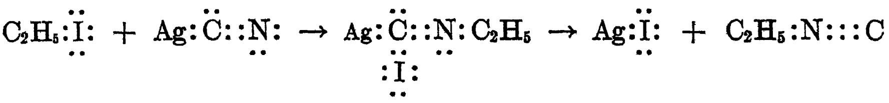
The reaction is commonly conducted in a boiling aqueous alcoholic solution of such concentration that both the halide and the alkali cyanide are dissolved. When insoluble metal cyanides such as copper cyanide are used, a non-aqueous system is preferred, frequently without solvent.

The reaction is almost always accompanied by the production of a certain amount of the isomeric isocyanide. The ratio of isocyanide to nitrile depends largely on the nature of the metal cyanide employed. Guillemard (231), in an extensive study of different metal cyanides, showed that the heavier metal cyanides such as those of silver gave isocyanides exclusively, while with other metals the following percentages of isocyanide were in the mixture resulting from the reaction with ethyl iodide: cuprous copper, 56 per cent; cadmium, 11 per cent; nickel, 8 per cent; zinc, 2.6 per cent. Sodium and potassium cyanides gave only minor amounts of isocyanides. The temperature of reaction was also found to play an important rôle in the amount of isocyanide produced. All of the metallic cyanides gave normal nitriles if the reaction were conducted above 150°C. Lower temperatures favored isocyanide formation. The thermal effect was substantiated by studies of the isomerization of isocyanides in the absence of metallic cyanides. These findings led Guillemard to the hypothesis that the reaction always led primarily to the isocyanide, which underwent rearrangement in certain cases.

Gautier (204) and Hartley (246) have observed that methyl iodide forms molecular complexes with one or two moles of silver cyanide but not with alkali cyanides. Decomposition of these complexes led to the isocyanide. It has been suggested that sodium cyanide is ionic in nature and reacts with ethyl iodide by an ionic mechanism.

$$C_2H_5I + CN^- \rightarrow C_2H_5CN + I^-$$

However, silver cyanide and cuprous cyanide have essentially covalent bonds and the reaction proceeds through the formation of an intermediate complex (454).



$$C_2H_5{:}\underset{\cdot\cdot}{\overset{\cdot\cdot}{I}}{:} + Ag{:}\overset{\cdot\cdot}{C}{::}\underset{\cdot\cdot}{N}{:} \rightarrow Ag{:}\underset{\underset{\cdot\cdot}{:I:}}{\overset{\cdot\cdot}{C}}{::}\underset{\cdot\cdot}{N}{:}C_2H_5 \rightarrow Ag{:}\underset{\cdot\cdot}{\overset{\cdot\cdot}{I}}{:} + C_2H_5{:}N{:::}C$$

This view was recently substantiated by Gallais (206), who concluded from studies of the ultraviolet absorption spectra that the basic difference between sodium cyanide and silver cyanide was that the former was a simple salt while the latter existed as a covalent complex, $Ag[Ag(CN)_2]$. It appears that Guillemard's hypothesis of primary isocyanide formation does not account for all of the facts and contributes very little to an understanding of the different reaction mechanisms.

Ogg (441) has calculated from available data the heat of reaction and experimental activation energies of the reaction of methyl halides with the cyanide ion in aqueous solution. Data for a few other exchange reactions are included in table 1 for comparison.

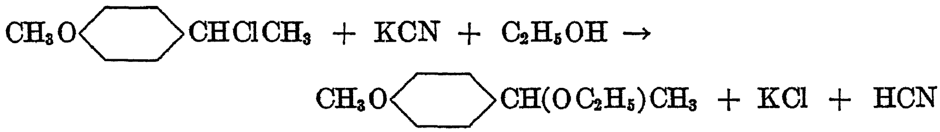
Purification of the nitriles produced in these reactions is facilitated by the fact that isocyanides are rapidly hydrolyzed to formic acid and the amine by treatment with cold dilute acids (231). Hence washing the product with hydrochloric acid usually suffices to remove isocyanide impurities, the presence of which is easily detected by their characteristic offensive odor.

In addition to isocyanide formation, other side-reactions often occur in the reaction of organic halides with alkali cyanides in aqueous alcohol. A certain amount of hydrolysis of the product usually occurs under the basic conditions which obtain. In a large number of cases the hydrolysis is deliberately promoted by long heating at high temperatures to obtain the acids directly. The classic syntheses of tricarballylic acid from 1,2,3-tribromopropane (525), fumaric acid from 1,2-diiodoethylene (308), and citric acid from the cyanohydrin of *sym*-dichloroacetone (229) are illustrative of this technique. The nitrile is also frequently contaminated by the alcohols or ethers resulting from hydrolysis or alcoholysis of the halide reagent by the solvent under the influence of the basic alkali cyanide. In the case of the reaction of *p*-(α-chloroethyl)anisole with alcoholic potassium cyanide a nearly quantitative yield of the ethyl ether resulted and none of the expected nitrile was obtained (468).

TABLE 1

Heat of reaction of methyl halides with cyanide ion

REACTION	HEAT OF REACTION	ACTIVATION ENERGY
	kg.-cal./mole	*kg.-cal./mole*
$CH_3Cl + CN^-$	+19.8	22
$CH_3Br + CN^-$	+18.2	22
$CH_3I + CN^-$	+19.4	22
$CH_3Cl + OH^-$	+18.0	23
$CH_3Cl + C_2H_5O^-$	+17.1	21
$CH_3Cl + C_6H_5O^-$	+13.4	19.5
$CH_3Cl + CH_3COO^-$	+10.2	22.3
$CH_3Cl + SH^-$	+19.7	28



Of the *alkyl halides*, the iodides react most readily. The bromides and chlorides react quite readily, while the fluorides appear to be inert. The yield and rate of the reaction of an alkyl chloride with an alkali cyanide may be improved by the addition of an alkali iodide as a promotor (248).

The reaction of normal alkyl iodides with potassium cyanide has served for the progressive synthesis of higher homologues by the following scheme:

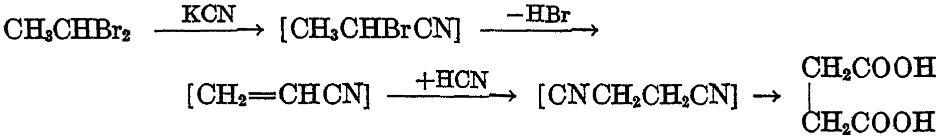
$$RCOOR \rightarrow RCH_2OH \rightarrow RCH_2I \rightarrow RCH_2CN \rightarrow RCOOH$$

By this method, Levene and Taylor have synthesized progressively the nitriles containing from nineteen to twenty-six carbon atoms (359).

Variation in the structure of the alkyl group affords a great difference in reactivity. Thus, primary halides usually react readily, while secondary and tertiary halides usually give dehydrohalogenation products with liberation of hydrogen cyanide from the alkali cyanide. Hass and Marshall found that *n*-amyl chloride reacted with sodium cyanide in 70 per cent conversion and about 95 per cent yield. Secondary amyl chloride, on the other hand, gave about 30 per cent yields and tertiary amyl chloride gave only the olefin (248). This difficulty may sometimes be obviated by using a non-basic metallic cyanide. In general, alicyclic halides also give olefins, although the conversion of cyclopentyl bromide to the nitrile has been accomplished with sodium cyanide in 27 per cent yield (491).

Compounds of the neopentyl halide type are remarkably inactive. Franke was unable to obtain nitriles by the action of potassium cyanide on 2,2-dialkyl-1,3-dibromopropanes (194), while neopentyl chloride was recovered unchanged after contact with cuprous cyanide at 90°C. for 200 hr. (592).

The conversion of *dihalides* to nitriles is influenced by the fact that a cyano substituent apparently activates a halogen removed from it by an even number of carbon atoms, and slightly inhibits the halogen atoms separated from it by an odd number of carbon atoms. Thus, the first cyano group to enter a molecule influences the ease with which the second halogen atom is replaced. Attempts to convert methylene halides or chloroacetonitrile to malononitrile have been unsuccessful (419), although ethylidene bromide has been partially converted to succinic acid probably through the successive steps of metathesis, dehydrobromination, addition of hydrogen cyanide, and hydrolysis.



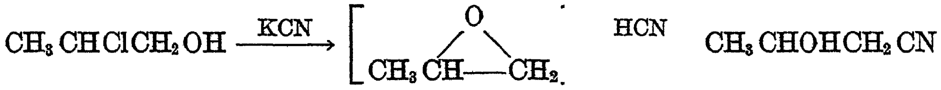
$$CH_3CHBr_2 \xrightarrow{KCN} [CH_3CHBrCN] \xrightarrow{-HBr} [CH_2{=}CHCN] \xrightarrow{+HCN} [CNCH_2CH_2CN] \rightarrow \begin{array}{l} CH_2COOH \\ | \\ CH_2COOH \end{array}$$

Ethylene dibromide, however, is smoothly converted to succinonitrile by sodium cyanide in refluxing aqueous ethanol (177), but β-bromopropionitrile cannot be isolated when a deficiency of sodium cyanide is used (419). Although ethylene dichloride will not react in this solvent even at 180°C. under pressure, β-chloropropionitrile is rapidly converted in excellent yields to succinonitrile at 40°C. (419). A two-step dehydrohalogenation–hydrogen cyanide addition mechanism could be advanced to explain the high reactivity of β-chloropropionitrile. However, this mechanism cannot account for the behavior of the isomeric xylylene dibromides described in the following paragraph. The conversion of 1-chloro-3-bromopropane to γ-chlorobutyronitrile (6) illustrates the difference in reactivity of different halogens, while the absence of appreciable quantities of glutaronitrile gives further evidence of the inhibiting action of a cyano group in the 3-position. Similarly, the only product isolated from the reaction of sodium cyanide and 1,3-dichloro-2-propanol was 3-chloro-2-hydroxybutyronitrile (69). However, an increased reaction time and an excess of potassium cyanide did permit the formation of an 11 per cent yield of β-methylglutaronitrile from 1,3-dichloro-2-methylpropane, although the main product was the chloronitrile (123). Tetramethylene chloride or bromide, on the other hand, is smoothly converted to adiponitrile in very high yield (515), and this synthesis is reported to have been adopted in commercial production in Germany in recent years (151).

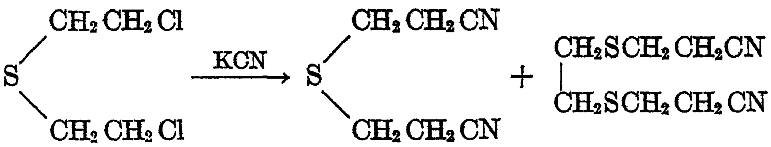
The alternating activation of halides by the cyano group is apparently transmitted through aromatic rings. Thus, two groups of investigators showed that *o*- and *p*-xylylene dibromides are converted only to dinitriles. No bromonitrile could be detected in the products, even when a deficiency of potassium cyanide was employed. On the other hand, the use of an excess of potassium cyanide failed to convert the meta isomer to the dinitrile, although the bromonitrile was obtained in 90 per cent yield (220, 605). 1,2,4-Tris(chloromethyl)benzene has been similarly converted to the trinitrile (340).

The tendency toward inhibition appears to diminish as the intervening chain length increases. α,ω-Dinitriles from seven to thirty-four carbon atoms in length have been smoothly synthesized in high yields from potassium cyanide and the dibromides (71, 74, 112, 623).

Haloalcohols are converted in aqueous or alcoholic solution to hydroxynitriles. Ethylene chlorohydrin, for example, reacts smoothly at moderate temperatures to give 85–95 per cent yields of ethylene cyanohydrin (33). This reaction was for many years the basis of the commercial synthesis of this intermediate for acrylonitrile. Other olefin chlorohydrins react similarly (180, 317). Dewael made the interesting observation that 2-chloropropanol was converted in 60 per cent yield by alcoholic potassium cyanide to β-hydroxybutyronitrile instead of the expected β-hydroxyisobutyronitrile (158). He concluded that the reaction proceeded by dehydrohalogenation to propylene oxide and that this intermediate then added hydrogen cyanide in the normal fashion.

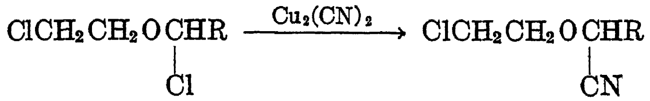


Since reactions similar to those hypothesized are known to take place under conditions obtaining in the experiment, it is reasonable to suspect that this mechanism may be operative in the reaction of all olefin chlorohydrins with alkali cyanides. Derivatives of chloroalcohols such as ethers (449, 462), thioethers (121), and esters (419) usually react normally. Similar behavior is exhibited by amidoalkyl chlorides (72) and aminoalkyl chlorides (121). An unexpected by-product was observed in the case of the reaction of bis(β-chloroethyl) sulfide (mustard gas) and potassium cyanide (43).



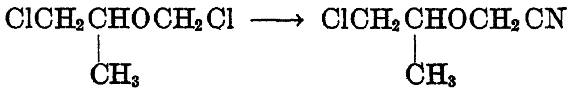
Its formation was explained by a side-reaction of the intermediate chloronitrile, through a sulfonium salt mechanism.

If the halogen is attached to a carbon atom bound to an oxygen atom, as in α-chloroalkyl esters (85) or ethers, a pronounced activation is noted. In most of these cases copper, mercury, or silver cyanides have been used because of the tendency of aqueous alkali cyanides to promote cleavage of the carbon–oxygen bond, while anhydrous alkali cyanides are usually unreactive. A large number of chloromethyl ethers have been converted to cyanomethyl ethers, notably by Henze and coworkers (8, 89, 212, 260, 533). The reaction is commonly effected in boiling benzene or ether and yields of 55–80 per cent are reported. The yields of higher α-cyanoalkyl ethers decrease with increasing chain length (364). For the reaction



$$\underset{\displaystyle Cl}{ClCH_2CH_2OCHR} \xrightarrow{Cu_2(CN)_2} \underset{\displaystyle CN}{ClCH_2CH_2OCHR}$$

the yields of nitriles were as follows: R = H (50 per cent); R = CH_3 (41 per cent); R = C_2H_5 (38 per cent); R = C_3H_7 (35 per cent). The above reaction also illustrates the activating influence of the ether linkage on a halogen in the α-position. The second halogen, in the β-position, is not replaced, although bis-chloromethyl ethers are converted to dinitriles under similar conditions (8). A similar effect was noted in the following reaction, which was effected in 81 per cent yield by means of cuprous cyanide and in 65 per cent yield by means of mercurous cyanide (537):



$$\underset{\displaystyle CH_3}{ClCH_2CHOCH_2Cl} \longrightarrow \underset{\displaystyle CH_3}{ClCH_2CHOCH_2CN}$$

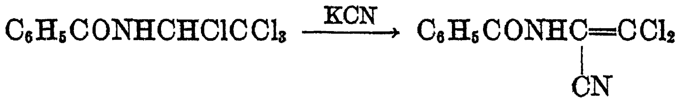
α,β-Dibromoethyl alkyl ethers (25, 463) and α,β-dichloroethyl acetate (419) react with cuprous cyanide in 40–50 per cent yields.

$$CH_2BrCHBrOR \xrightarrow{CuCN} CH_2BrCH(CN)OR$$

Potassium cyanide effects a similar reaction together with cleavage of the ether group, and β-chlorolactonitrile is obtained in 24 per cent yield (278, 419).

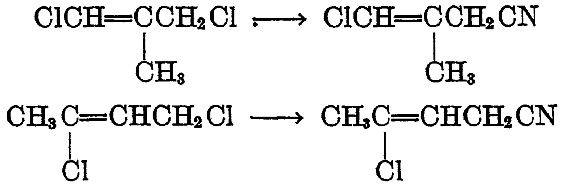
$$CH_2ClCHClOC_2H_5 \xrightarrow{KCN} CH_2ClCHOHCN$$

Similar activation is conferred upon a chlorine atom attached to a carbon adjacent to a nitrogen atom. In the following case, dehydrohalogenation accompanies the metathesis reaction (267).



$$C_6H_5CONHCHClCCl_3 \xrightarrow{KCN} C_6H_5CONH\underset{\displaystyle CN}{C}{=}CCl_2$$

Unsaturated alkyl halides are affected by additional complicating factors in their reactions with metal cyanides. If the halide is of the vinyl type, its reactivity is greatly diminished. This difference is illustrated by the reactions of the following dichloroölefins in which the halogen attached to the olefinic carbon is not replaced (123, 128).

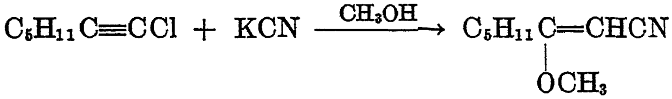


$$\mathrm{ClCH{=}\underset{\displaystyle CH_3}{C}CH_2Cl \longrightarrow ClCH{=}\underset{\displaystyle CH_3}{C}CH_2CN}$$

$$\mathrm{CH_3\underset{\displaystyle Cl}{C}{=}CHCH_2Cl \longrightarrow CH_3\underset{\displaystyle Cl}{C}{=}CHCH_2CN}$$

The use of bromides or iodides with cuprous cyanide at temperatures of 150–250°C. enables some α,β-unsaturated nitriles to be prepared. These conditions, which are reminiscent of those obtaining in the Rosenmund-von Braun aromatic nitrile synthesis (see pages 207–208) were used by Jennen (293) to prepare fumaronitrile from *sym*-diiodoethylene. The dibromo- and dichloro-ethylenes will not react below the decomposition temperature of the product. A trace of a tertiary amine acts as a promotor in this reaction and enables the yields to be raised from 30 to 75 per cent (268). Koelsch has applied this technique to the preparation of α,β,β-triphenylacrylonitrile and related compounds from the appropriate vinyl bromides (315).

Acetylenic halides on the other hand react readily with methanolic potassium cyanide, but the sole product is the cyanoether which results from addition of the alcohol to the intermediate nitrile (413).



$$\mathrm{C_5H_{11}C{\equiv}CCl + KCN \xrightarrow{CH_3OH} C_5H_{11}\underset{\displaystyle OCH_3}{C}{=}CHCN}$$

No reaction takes place in dioxane solution, even if the bromo- or iodo-acetylene is used (373).

Allylic halides are also very reactive but introduce complications caused by two types of isomerization, *viz.*, migration of the double bond and 1,3- or 1,5-anionotropic rearrangements. Early workers assumed that the reaction product of allyl bromide and potassium cyanide was allyl cyanide, but it was later shown that isomerization to crotononitrile had taken place (20, 448, 459). The reaction will not proceed in the absence of a trace of water even at 120°C. (459). In alcoholic solution, by-products formed include β-ethoxybutyronitrile (488) and methyl succinonitrile (457). These arise from the addition of alcohol and hydrogen cyanide to the reactive α,β-double bond under the alkaline conditions which obtain. The side-reactions caused by the basic reagent are avoided by the use of cuprous cyanide, and very high yields of the unisomerized product are obtained (79, 258). A trace of pyridine serves to eliminate the induction period which occurs when very pure reagents are used (431a). This technique has been applied to the preparation of numerous cyanides of the allyl type (154). Apparently rearrangements do not always take place with alcoholic alkali cyanides, since no shifting of the double bond was detected in the conversion of 3-chlorocyclopentene to the nitrile by potassium cyanide in aqueous alcoholic solution (146).

Dihalides of the allyl type, such as 1,4-dichloro-2-butene, react readily with potassium cyanide to give some of the normal product, dihydromucononitrile, but the principal product is 1-cyano-1,3-butadiene which arises through dehydrohalogenation of the intermediate chloronitrile (105, 235).

$$\mathrm{ClCH_2CH{=}CHCH_2Cl + 2KCN \rightarrow CNCH_2CH{=}CHCH_2CN\ (5\text{–}20\ per\ cent) + CH_2{=}CH{-}CH{=}CHCN\ (13\text{–}70\ per\ cent)}$$

Increased yields of the dinitrile are stated to be obtained if the reaction is run in the absence of air and in the presence of a solvent such as acetonitrile (335). Surprisingly, 1,4-dichloro-2-butyne is inert to the action of either potassium cyanide or cuprous cyanide (295).

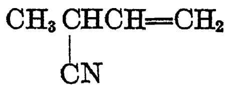
1-Chloro-2,3-butadiene undergoes many metathetical reactions without undergoing rearrangements, but with potassium cyanide in methanol the isomerized product is obtained, together with some 5-methoxy-3-pentenonitrile arising from 1,4-addition of the solvent.

$$\mathrm{CH_2{=}C{=}CHCH_2Cl + KCN \xrightarrow{CH_3OH} CH_2{=}CHCH{=}CHCN + CH_3OCH_2CH{=}CHCH_2CN}$$

No 2-cyano-1,3-butadiene, which would be expected to arise by 1,3-anionotropic rearrangement, was detected (127).

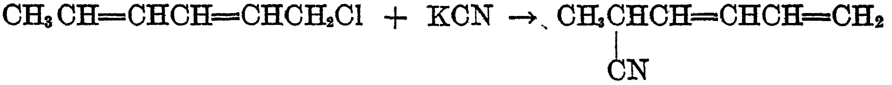
Lane, Fentress, and Sherwood observed that when 1-chloro-2-butene reacts with cuprous cyanide an allylic rearrangement takes place, so that the product is a mixture of 91.5 ± 0.5 per cent 1-cyano-2-butene and 8.5 ± 0.5 per cent 2-cyano-3-butene. The same ratio of product isomers is obtained if the starting materials are 90 per cent 2-chloro-3-butene and 10 per cent 1-chloro-2-butene or 80 per cent 2-bromo-3-butene and 20 per cent 1-bromo-2-butene. The reacting chlorides easily undergo the allylic rearrangement, but the equilibrium mixture consists of 74 per cent of the primary chloride and 26 per cent of the secondary chloride. The product nitriles do not rearrange under the conditions of the experiment. The authors conclude from the above data that the reaction proceeds through a mesomeric carbonium ion and is not a simple bimolecular substitution (349).

$$\mathrm{CH_3CH{=}CHCH_2X + CH_3CHXCH{=}CH_2 \rightarrow X^- + [CH_3CH{\overset{...}{-}}CH{\overset{...}{-}}CH_2]^+ \xrightarrow{CN^-} CH_3CH{=}CHCN\ (91.5\ per\ cent) +}$$



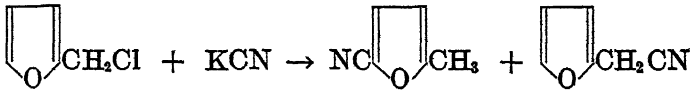
$$\mathrm{CH_3CH(CN)CH{=}CH_2}\ (8.5\ \text{per cent})$$

A similar rearrangement has been reported for the reaction of sorbyl chloride and potassium cyanide, but the anionotropic rearrangement here is of the 1,5-type (480).



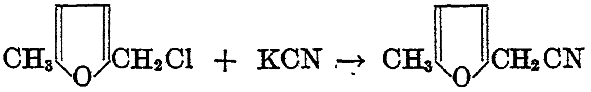
$$CH_3CH{=}CHCH{=}CHCH_2Cl + KCN \rightarrow \underset{\displaystyle CN}{\underset{|}{CH_3CH}}CH{=}CHCH{=}CH_2$$

The reaction between furfuryl chloride and potassium cyanide was originally assumed to give furylacetonitrile. Runde, Scott, and Johnston (498, 523) and Reichstein (478) independently discovered that only a small amount of this product is obtained. The major product is 5-methylfuronitrile, the result of a 1,5-rearrangement.



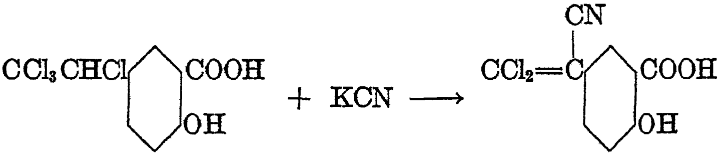
(85 per cent) (15 per cent)

A similar rearrangement takes place with α-(1-chloroethyl)furan (482), but 5-methylfurfuryl chloride is converted without appreciable rearrangement (481, 523).



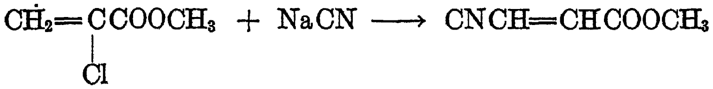
Benzyl chloride and thenyl chloride give only the normal products (387).

Halides of the benzyl type are converted very readily to arylacetonitriles in 80–90 per cent yields with alkali cyanides in water or aqueous alcohols at reflux (383, 419). α-Chloromethylnaphthalene gives similar results (122, 384). Carbethoxy (406) and phthalide (107) substituents on the aromatic nucleus were unaffected by the reagent. However, 5-(α,β,β,β-tetrachloroethyl)salicyclic acid underwent both metathesis and dehydrohalogenation (159).



The principal by-products are arylcarbinols, arylacetamides, and ethers which arise through reaction with the solvent. Side-reactions do not become very serious except in the case of especially reactive halogen atoms. Most of these cases involve alkylbenzyl or alkoxybenzyl halides or benzohydryl halides. The formation of ethers was eliminated in the case of 1-chloromethyl-2-methoxynaphthalene by reacting it with potassium cyanide in 66 per cent acetone solution at 30–35°C. (133). The use of cyanides of the heavy metals, such as mercuric cyanide in acetonitrile solution, gives similar results (607). Cuprous cyanide in pyridine (202) or phenylacetonitrile (263) solution has given good results. The reaction of *p*-methoxybenzyl chloride and cuprous cyanide, however, yields only tars reminiscent of the polymers obtained from benzyl chloride and acidic metal chlorides. However, benzyl chloride itself is converted to phenylacetonitrile in 71 per cent yield under the same conditions (587).

Halides containing halogen alpha to a carboxyl group are also highly reactive toward alkali cyanides. Thus, sodium chloroacetate is transformed almost instantaneously to sodium cyanoacetate in cold aqueous solution. Conversion of methyl esters is conveniently accomplished with methanolic potassium cyanide (439). Although it was noted earlier that a halogen was relatively inactive if attached to an ethylenic carbon atom, this influence is counterbalanced by the presence of an α-carbethoxy group. For example, methyl α-chloroacrylate reacts readily with sodium cyanide to give methyl β-cyanoacrylate (137, 418).



$$CH_2{=}\underset{\mathrm{Cl}}{\underset{|}{C}}COOCH_3 + NaCN \longrightarrow CNCH{=}CHCOOCH_3$$

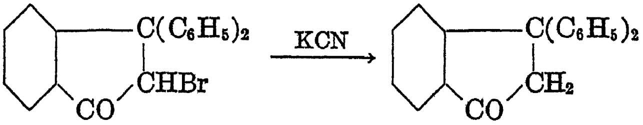
The fact that a rearrangement has taken place indicates that the mechanism must involve a 1,4-addition of hydrogen cyanide to the carbonyl–olefin conjugated system and removal of the chlorine by dehydrohalogenation. α-Chloroacrylonitrile reacts in a strictly analogous fashion, but esters of chloromaleic, chlorofumaric, and α-chlorocrotonic acids appear to be inert (108, 419).

Certain *halides containing halogen alpha to a carbonyl group* react normally. Thus, ethyl α-bromopropionate and alcoholic potassium cyanide are converted to ethyl α-cyanopropionate (547). Phenacyl halides and many of their nuclear-substituted derivatives appear to give the normal reaction (82, 469).

$$C_6H_5COCH_2X + KCN \longrightarrow C_6H_5COCH_2CN$$

α-Bromohydrindone (297) and α-bromopinacolone (596) are similarly converted to the β-ketonitriles.

In many cases, especially if the halide is secondary, dehydrohalogenation or reduction (with replacement of the halide by hydrogen) occurs. Thus, 2-bromo-3,3-diphenylhydrindone (204),



and benzalacetophenone dihalides (264, 427)

$$C_6H_5COCHClCHClC_6H_5 \xrightarrow{KCN} C_6H_5COCH_2CH(C_6H_5)CN$$

are smoothly converted to the reduced forms. In the latter case, reduction appears to be followed by dehydrohalogenation to benzalacetophenone, which can be isolated at low temperatures. Addition of hydrogen cyanide to the unsaturated ketone then proceeds in the normal fashion.

The action of alcoholic potassium cyanide on chloral and related compounds has been studied in detail by Chattaway and Irving (108). This reaction results in simultaneous reduction of one of the α-chlorine atoms and conversion of the aldehyde group to a carbethoxy group.

$$CCl_3CHO + KCN + C_2H_5OH \xrightarrow{(88\%\ \text{yield})} CHCl_2COOC_2H_5 + KCl + HCN$$

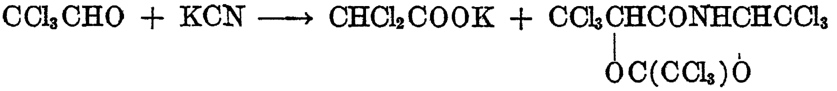
Use of other alcohols as solvents results in the formation of the corresponding esters. Dichloroacetaldehyde and monochloroacetaldehyde are similarly converted to esters of chloroacetic acid and acetic acid, respectively. Butyrochloral reacts similarly, but above 15°C. dehydrohalogenation also occurs.

$$CH_3CHClCCl_2CHO + KCN + C_2H_5OH \longrightarrow CH_3CHClCHClCOOC_2H_5 \xrightarrow{KCN} CH_3CH{=}CClCOOC_2H_5$$

The use of chloral diacetate gives analogous results, and the corresponding aldehyde ammonia derivatives are converted to the amides in 93 per cent yield.

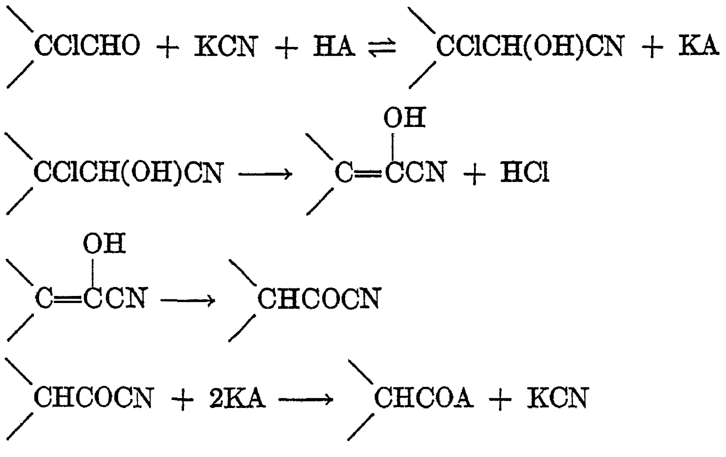
$$CCl_3CH(OH)NH_2 + KCN \longrightarrow CHCl_2CONH_2$$

Chloral and potassium cyanide in aqueous solution lead to potassium dichloroacetate, together with a high-melting by-product which is thought to be 6-keto-2,4,7-tris(trichloromethyl)-1,3,5-dioxazaseptane (138).



$$CCl_3CHO + KCN \longrightarrow CHCl_2COOK + \underset{OC(CCl_3)O}{CCl_3CHCONHCHCCl_3}$$

These transformations are thought to proceed through the cyanohydrin by a mechanism proposed by Pinner (458) and Kötz (320) and later substantiated by Lapworth (126). In the following generalized expression HA may represent water, alcohols or ammonia, and amines:



$$>CClCHO + KCN + HA \rightleftharpoons >CClCH(OH)CN + KA$$

$$>CClCH(OH)CN \longrightarrow >C{=}C(OH)CN + HCl$$

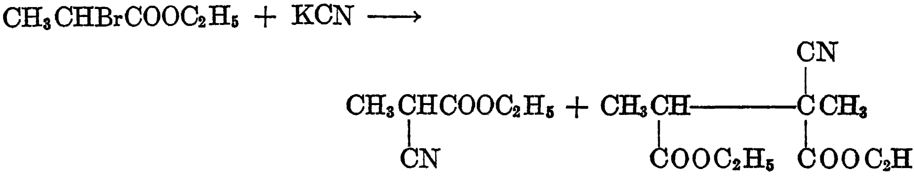
$$>C{=}C(OH)CN \longrightarrow >CHCOCN$$

$$>CHCOCN + 2KA \longrightarrow >CHCOA + KCN$$

$$HCl + KCN \longrightarrow KCl + HCN$$

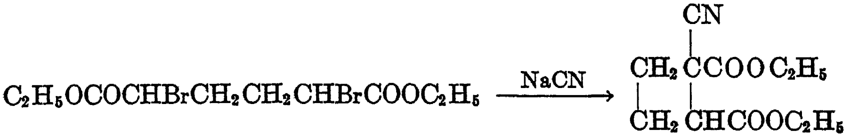
A strong argument for the cyanohydrin intermediate in the Pinner–Kötz mechanism is based on the fact that other materials of similar alkalinity do not effect the transformation. The diethyl acetals of chloral and related compounds are inert in this reaction because of the stability of the acetal linkage to basic media.

Halides containing halogen alpha to a carbonyl group often react with alkali cyanides to give inter- or intra-molecular dehydrohalogenation with the formation of a new carbon–carbon bond. Thus, by-products in the reaction of α-bromopropionic esters are the α,α'-dimethyl-α-cyanosuccinates (619).

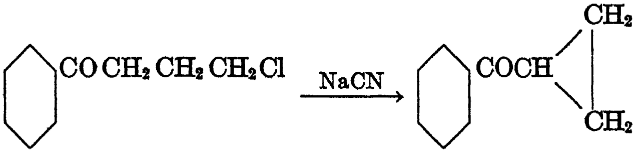


$$\mathrm{CH_3CHBrCOOC_2H_5 + KCN \longrightarrow \underset{CN}{\underset{|}{CH_3CH}}COOC_2H_5 + CH_3\underset{COOC_2H_5}{\underset{|}{CH}}\text{———}\overset{CN}{\overset{|}{\underset{COOC_2H_5}{\underset{|}{C}}}}CH_3}$$

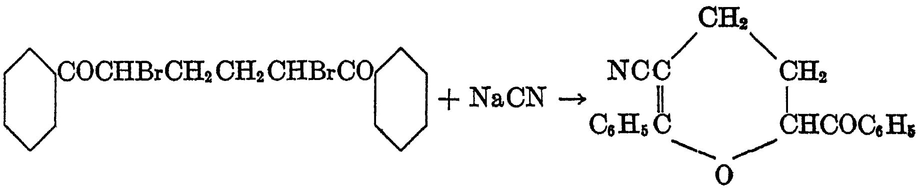
α-Chloroethyl methyl ketone gives a similar by-product (294). α,α'-Dibromoadipates are converted to cyclobutane derivatives (199, 338).

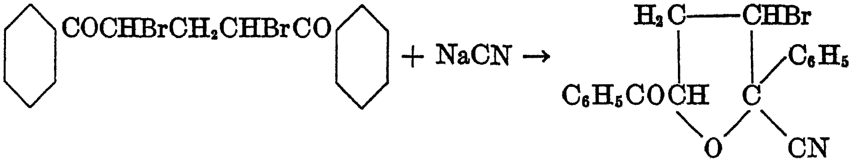


γ-Chlorobutyrophenone is similarly transformed into a cyclopropane derivative (5).

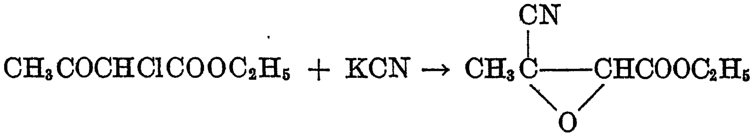


Dehydrohalogenation often occurs with the formation of a new epoxy linkage. This can arise either from the enol form of the ketone or from its cyanohydrin (200, 201).

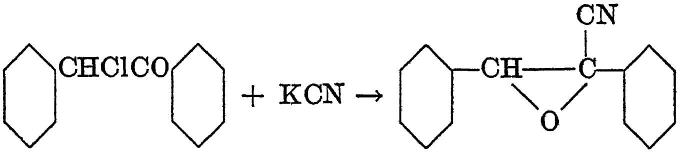




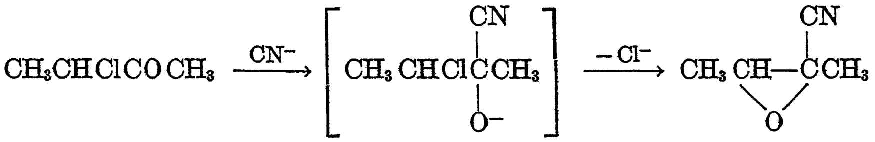
Early investigators assumed that the products resulting from the reaction of α-chloroketones and alkali cyanides were the normal β-ketonitriles. Actually in most cases, especially if the halide has a secondary configuration, the product is a cyanoölefin oxide. Thus, Favrel and Prevost demonstrated in 1931 that the product from α-chloroacetoacetic ester and potassium cyanide was not the cyanoketo ester, but ethyl α,β-epoxy-β-cyanocrotonate (178).



Desyl chloride reacts similarly (322).

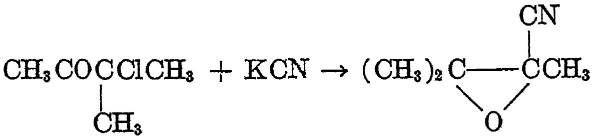


Other chloroketones which have been recently reported to react in this anomalous fashion are α-chlorobenzyl alkyl ketones (468), 2-chloro-3-butanone (215, 300), chloroacetone (300), and γ-chloroacetoacetic ester (318). It is probable that the cyanide ion attacks the carbonyl carbon, followed by elimination of the chloride ion through formation of the epoxide linkage.

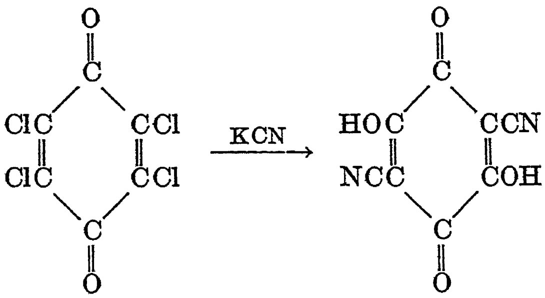


The cyanohydrin of the chloroketone is definitely not the intermediate, since Gerbaux (215) treated this compound (which he isolated by another method) with potassium cyanide and obtained very little of the cyanoepoxide, which was obtained in 70 per cent yield when the chloroketone was used.

Delbaere obtained a cyanoepoxide from 2-chloro-2-methyl-3-butanone. The reaction product in this case was further complicated by the occurrence of a pinacolone-type rearrangement (155).



Olefinic chlorine atoms, if activated by a carbonyl group, will react with potassium cyanide. In the case of chloranil, two of the halogens are replaced and two are hydrolyzed by the basic aqueous solution (487).



2. Aromatic halides

In 1877, Merz obtained α-naphthonitrile from α-bromonaphthalene by treatment with potassium ferrocyanide (395). A modified technique involved passing the gaseous aryl halide over the hot ferrocyanide at about 350–400°C. (12). Benzonitrile was also obtained from iodobenzene and silver cyanide (395), but the method has little preparative value.

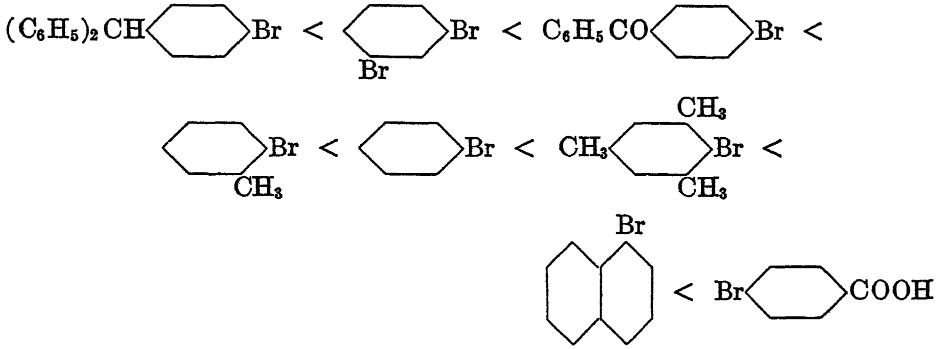
The use of cuprous cyanide dissolved in cyclic aromatic amines was introduced in the German patent literature in 1913 (12, 390). A related reaction was the conversion of bromobenzene to benzonitrile in 23 per cent yield by the action of copper thiocyanate in pyridine solution (493). Considerable diphenyl sulfide was obtained as a by-product.

Later de Diesbach extended the cuprous cyanide reaction and reported yields of 88 per cent for the conversion of a mixture of dibromoxylenes to the dinitriles (162). This technique has proved very popular with later workers. The aryl bromide and a slight excess of dry cuprous cyanide are added to sufficient dry pyridine or quinoline to form a homogeneous complex at reaction temperatures of 150–250°C. Aryl chlorides undergo the reaction satisfactorily if sufficiently activated by appropriate substituents. Thus, Newman converted α-bromonaphthalene with cuprous cyanide in pyridine solution to α-naphthonitrile in 93 per cent yield at 220°C. in 15 hr. α-Chloronaphthalene underwent 92 per cent conversion at 250°C. in 24 hr. (70 per cent in 6 hr.) (431). There appears to be an optimum time and temperature for each type of compound. For example, a substituted chlorobenzene is reported to give an 87 per cent yield at 245°C. in 25 hr., 74 per cent in 35 hr., and 67 per cent in 48 hr. In 60 hr. at 255°C. the yield dropped to 20 per cent (192).

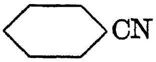
Another technique involves the use of cuprous cyanide in the absence of basic solvents. Thus, Rosenmund observed in 1919 that the addition of cuprous cyanide to aqueous sodium cyanide in the aryl halide reaction exerted a marked catalytic effect and considerably increased the yields of acids formed (494). The nitriles themselves are reported to be obtainable from the mixed sodium cyanide–copper cyanide reagent in the absence of water (217). The efficacy of copper catalysts has been similarly observed in the conversion of chlorobenzene to benzonitrile by zinc cyanide. Similarly, the use of copper, nickel, or cobalt halide catalysts is stated to give high yields at 300°C. in 4 hr., while less than 50 per cent yields are obtained with the zinc cyanide alone (565). von Braun observed that bromo derivatives of high-boiling aromatic hydrocarbons are smoothly converted to the nitriles in very high yield by treatment with a slight excess of cuprous cyanide at 260°C. (76). This method, later called the Rosenmund–von Braun synthesis, has been studied in detail by Koelsch and Whitney (315, 319), who found that the reaction is autocatalytic. Thus, *p*-bromotoluene is only 15 per cent converted at 250°C. in 60 min. but 75 per cent converted in 90 min. Addition of a small amount of a nitrile to the reagents largely eliminates this induction period. Copper sulfate in small amounts also has a marked catalytic effect, while hydroquinone retards the reaction. This observation led to the hypothesis that only the divalent copper ion can react with the aryl halide to form a stable complex. The following mechanism has been proposed (319):

$$\mathrm{ArX} + \mathrm{Cu}^{++} \rightleftharpoons [\mathrm{ArX}\rightarrow\mathrm{Cu}]^{++}$$
$$\mathrm{Cu}^{+} + [\mathrm{ArX}\rightarrow\mathrm{Cu}]^{++} \rightarrow \mathrm{Cu}^{++} + [\mathrm{ArX}\rightarrow\mathrm{Cu}]^{+}$$
$$[\mathrm{ArX}\rightarrow\mathrm{Cu}]^{+} \rightarrow \mathrm{Ar}^{+} + \mathrm{CuX}$$
$$\mathrm{Ar}^{+} + \mathrm{CN}^{-} \rightarrow \mathrm{ArCN}$$

Gradual addition of the halide to the cuprous cyanide and catalysts promotes rapid conversion, since the reacting halide acts as a diluent. A considerable difference in the rate of reaction has been observed with aryl bromides of different structures. The following sequence of increasing reactivity has been established (315):



The above two techniques of aryl halide–copper cyanide reactions (with or without a basic solvent) have been discussed by Braun (78). For large-scale runs, as in commercial practice, the use of a solvent or an inert diluent is desirable to assist the dissipation of the heat of reaction. This may be either a solvent for the cuprous cyanide (pyridine, quinoline, or phenylacetonitrile) or a diluent such as nitrobenzene, dichlorobenzene, or naphthalene. In general, the use of a solvent enables the reaction to be effected at lower temperatures. Most bromo compounds will react at 130–180°C., active chlorides at 180–190°C., and inactive chlorides at 190–240°C. The following yields of nitriles are reported to be obtained from the bromides in pyridine solution (78):



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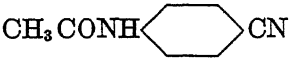

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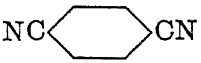

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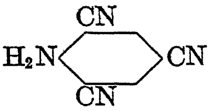

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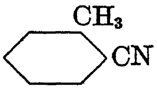

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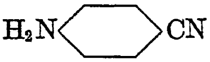

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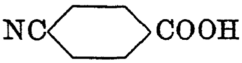
in *o*-dichlorobenzene solution:



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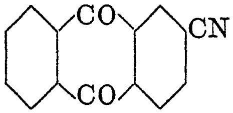
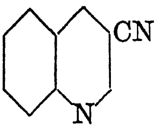


(93%)

and in nitrobenzene solution: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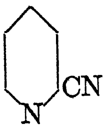
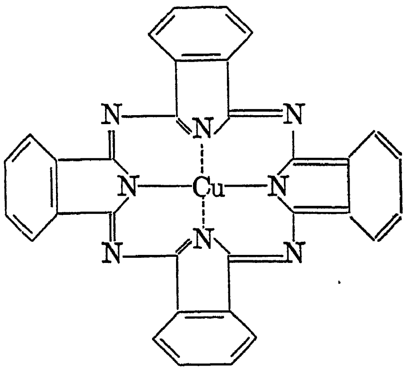

(90%)

Active aryl chlorides such as nitrochlorobenzenes, alkoxychlorobenzenes, polyalkylchlorobenzenes, 1-chloronaphthalenes, and 1-chloroanthraquinones are converted smoothly and in high yields under similar conditions (78).

An anomalous reaction was observed by Diesbach (163), who obtained a highly colored insoluble mass when *o*-dibromoxylene was reacted with copper cyanide in pyridine solution. The nature of these materials was elucidated by Linstead and coworkers, who showed them to be phthalocyanines or tetrabenzotetraazaporphins, a class of blue organic pigments which now have acquired considerable commercial importance (506).



Similarly, *o*-bromoacetophenone and other similar ortho derivatives lead to copper complexes of tetrabenzoazaporphins (255).

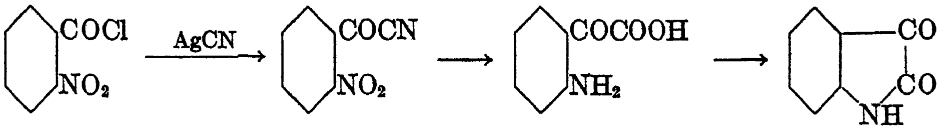
As would be expected, halogen derivatives of pyridine and quinoline react smoothly without solvents. The 4-, 5-, 6-, and 8-bromoisoquinolines are reported to be converted to the nitriles in 88, 81, 25, and 53 per cent yields, respectively (567).

The success of other transformations in the nitrogen heterocyclic series depends on the structures involved. Thus, 2-amino-4-methyl-5-bromopyrimidine was very rapidly converted to the nitrile (465), while 2-methyl-4-hydroxy-5-bromo-6-ethoxymethylpyrimidine was completely inert (372). On the other hand, 1-methyl-4-nitro-5-chloroglyoxaline was so reactive that an 85 per cent yield was obtained by the action of potassium cyanide in absolute alcohol (510).

3. Acid halides

As noted earlier, the first nitrile of recognized constitution to be synthesized was benzoyl cyanide, which Wöhler and Liebig made in 1832 by the distillation of benzoyl chloride over mercuric cyanide (609). The cyanides of mercury, silver (280a, 430), and copper (440, 565a) have continued to be the most useful reagents for the conversion of aroyl or acyl halides to the corresponding nitriles. When benzoyl chloride and dry cuprous cyanide are heated at 220–230°C. for 1.5 hr., a 60–65 per cent yield of benzoyl cyanide is obtained (440). The *o*-, *m*-, and *p*-phthalyl cyanides have been similarly prepared in 30–50 per cent yields by the action of mercuric chloride (49).

The method is equally applicable to the aliphatic series, but the lower-boiling acyl chlorides must often be treated with metallic cyanides under pressure. The acyl bromides are more reactive than the chlorides. Thus, acetyl bromide and cuprous cyanide are converted in 77 per cent yield to pyruvonitrile after 2 hr. on the steam bath, while acetyl chloride undergoes no reaction in 8 hr. (283). This reaction is applicable to a variety of types of halides, such as pentaacetylgluconyl chloride (13), acetyl mandelyl chloride (380), and disubstituted carbamyl chlorides (618). *o*-Nitrobenzoyl chloride was used in Claisen's classic synthesis of isatin (116):



Another interesting application of the acyl cyanide synthesis is found in Bouveault's preparation of aldehydes from acid chlorides (62):

$$\mathrm{RCOCl} \rightarrow \mathrm{RCOCN} \rightarrow \mathrm{RCOCOOH} \xrightarrow[-\mathrm{CO}]{\mathrm{C_6H_5NH_2}}$$

$$\mathrm{RCH{=}NC_6H_5} \xrightarrow{\mathrm{H_2SO_4}} \mathrm{RCHO}$$

Anhydrous alkali cyanides do not readily react under the above conditions (283). Most acyl cyanides, while capable of being hydrolyzed by mineral acids to α-ketoamides, are rapidly cleaved by aqueous bases to salts of the acids and hydrocyanic acid.

$$\mathrm{RCOCN} + \mathrm{NaOH} \rightarrow \mathrm{RCOONa} + \mathrm{NaCN}$$

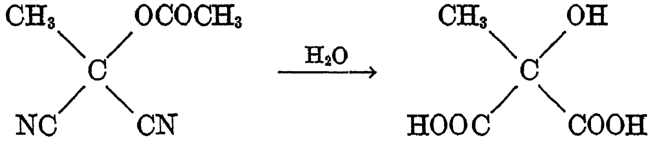
For this reason aqueous or alcoholic solutions of the basic alkali cyanides are rarely used for the conversion of acid halides to α-ketonitriles. However, by working rapidly at temperatures below 0°C. Nef was able to isolate benzoyl cyanide and alkyl cyanoformates (430). The phenylhydrazone of ethyl cyanoglyoxylate also appears to be sufficiently stable to alkaline cleavage to enable its preparation from the corresponding chloro compound and hot alkali cyanide solution (97).

Another popular synthesis of acid cyanides is the method of Claisen (113), who slowly added pyridine to anhydrous ether solutions of acid chlorides and hydrogen cyanide. The reverse order of addition favors the formation of acid cyanide dimers. The precipitation of pyridine hydrochloride from the ether solution aids in effecting high conversions.

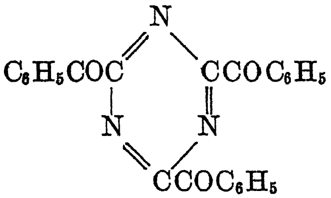
$$\mathrm{RCOCl} + \mathrm{HCN} + \mathrm{C_5H_5N} \rightarrow \mathrm{RCOCN} + \mathrm{C_5H_5N{\cdot}HCl}$$

The method is of general application, but aroyl cyanides are prepared in much better yields (40–80 per cent) than aliphatic acyl cyanides (161, 185, 291, 386, 554).

As implied above, a complication in the preparation of acyl or aroyl cyanides is the formation of low-molecular-weight polymers. Thus, in the preparation of benzoyl cyanide the monomer, m.p. 32°C., was obtained by the action of mercuric or cuprous cyanide on benzoyl chloride (430, 578); the dimer, m.p. 99–100°C., was obtained by the action of cold sodium cyanide or pyridinium cyanide on benzoyl chloride (161, 430); while the trimer, m.p. 195°C., was obtained from benzoyl bromide and silver cyanide in ether solution (430). The structure of the dimer (which can also be made from the monomer by the action of sodium in absolute ether) is obscure. In this connection, the dimer of pyruvonitrile, obtained from acetic anhydride and potassium cyanide, was shown to have the following structure by virtue of its hydrolysis to isomalic acid (86):



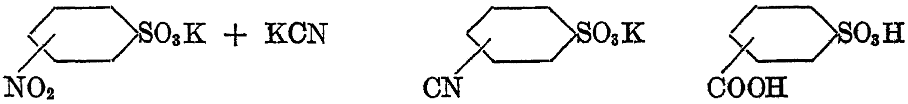
Benzoylcyanide trimer is probably 2,4,6-tribenzoyl-1,3,5-triazine.



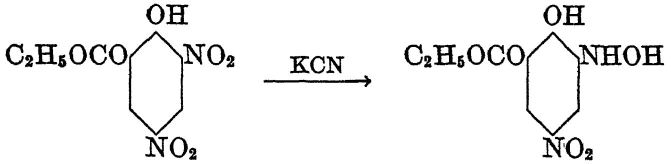
A recent patent indicates that acyl cyanides may be prepared in low conversion but good yield by the action of acid anhydrides on hydrogen cyanide at 240–270°C. (221a).

D. NITRO OR AMINO COMPOUNDS AND METAL CYANIDES

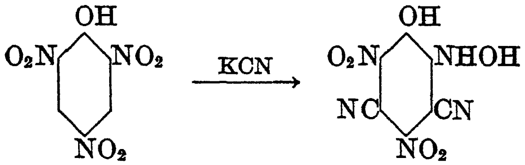
The replacement of nitro or amino groups by the action of metallic cyanides is not of general application. It will however be discussed briefly, since it appears to be an excellent preparative method for certain types of compounds. Fittig and Ramsay first observed that potassium nitrobenzenesulfonates were converted by hot aqueous potassium cyanide to a complex mixture of sulfonated carboxylic acids. The reaction must have proceeded through the unisolated nitrile intermediate (188).



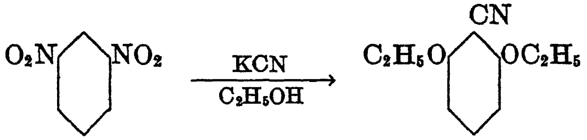
The compounds most amenable to reaction with potassium cyanide are the polynitrobenzenes and the polynitrophenols. The structure of the products of the latter reaction, loosely called "purpuric acids", has been elucidated principally by de Bruyn (93) and Borsche (57, 58). Four distinct types of action take place, often simultaneously: (*a*) reduction of a nitro group to an azo, azoxy, nitroso, or hydroxylamino group, (*b*) replacement of a nitro group by an alkoxy group if the reaction is conducted in alcoholic solution, (*c*) replacement of a hydrogen by the cyano group, and (*d*) replacement of the nitro group by the cyano group. The last type requires very reactive nitro groups. de Bruyn reports an example of an alkoxydinitrobenzonitrile being converted to a phthalonitrile derivative by the action of potassium cyanide (93). Representative examples of the other types of reactions are given below:



(57)

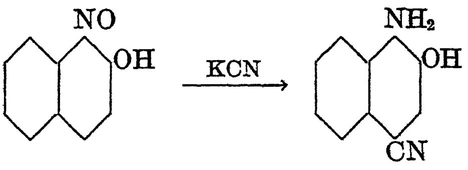


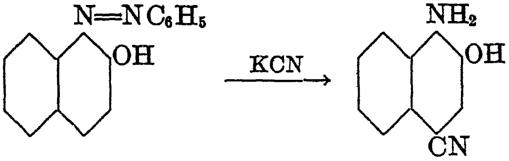
(57)



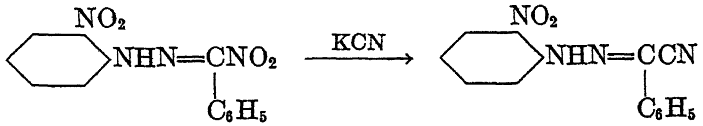
(566)

Nitroso- or azo-naphthols react similarly (65).

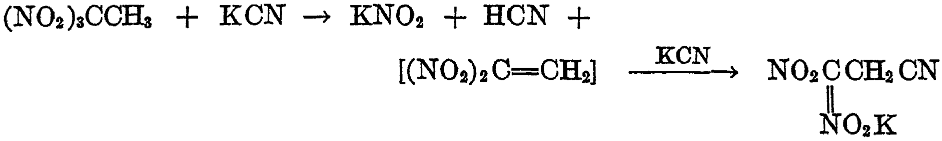




Reports of replacement of an aliphatic nitro group by a cyano group are rare. The *o*-nitrophenylhydrazone of phenylnitroformaldehyde reacts with potassium cyanide in refluxing alcohol (460).

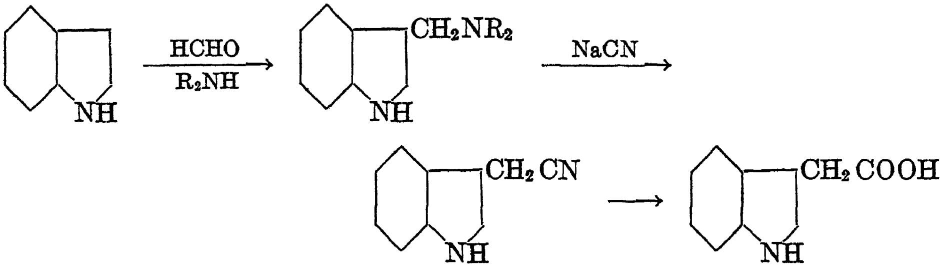


From 1,1,1-trinitroethane is formed the potassium salt of β,β-dinitropropionitrile. The reaction probably involves the formation of *asym*-dinitroethylene, followed by addition of potassium cyanide (389).



$$(NO_2)_3CCH_3 + KCN \rightarrow KNO_2 + HCN + [(NO_2)_2C{=}CH_2] \xrightarrow{KCN} NO_2\underset{\substack{\| \\ NO_2K}}{C}CH_2CN$$

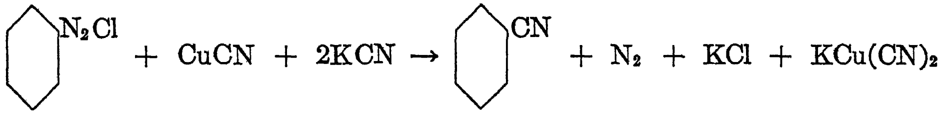
A synthesis of indoleacetic acid has recently been reported in which the key reaction is the conversion of 3-(dialkylaminomethyl)indole to indole-3-acetonitrile in 30 per cent yield by the action of sodium cyanide (505).



If this reaction proves to be typical of Mannich bases, it may be a very useful method for the introduction of a cyanomethyl group.

E. DIAZONIUM HALIDES AND METAL CYANIDES (SANDMEYER SYNTHESIS)

The preparation of aromatic nitriles by the reaction of cold solutions of diazonium salts with a cuprous cyanide–potassium cyanide solution was discovered by Sandmeyer in 1884 (507).



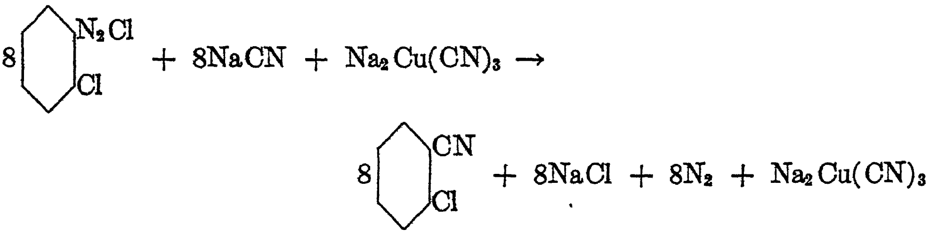
The Gattermann modification involving the use of an alkali cyanide and metallic copper was stated to be feasible (208), but apparently has not been widely adopted as a preparative method. Korczynski found in 1920 that the use of the double salt obtained from potassium cyanide and nickel cyanide gives equivalent or slightly better yields and purer products than the standard Sandmeyer technique (156, 326, 327, 499). This is one of the few instances in which a Sandmeyer reaction succeeds in the absence of cuprous salts. However, the cyanides of cobalt, iron, chromium, zinc, and numerous other metals are not effective.

Clarke and Reade found that the reaction could be effected in neutral or slightly basic solution. By neutralizing the excess acidity of the diazonium solution before addition to the cyanide solution slightly better yields are sometimes obtained and the liberation and loss of hydrogen cyanide by excessive acidity are avoided (118). Diazonium or tetrazonium borofluorides are converted to nitriles by treatment with the cyanide reagent (497).

Subsequent developments have been in the direction of decreasing the ratio of copper cyanide to diazonium compound. By the reaction of the diazonium solution with a sodium cupriammonium cyanide (prepared from copper sulfate, ammonium hydroxide, and sodium cyanide), Hagenest was able to reduce the consumption of both copper and sodium cyanide (234, 285). Yields of 65 per cent of benzonitrile and 83 per cent of *p*-tolunitrile based on the following equation are claimed:

$$3C_6H_5N_2Cl + Na_3Cu(CN)_5NH_3 \rightarrow 3C_6H_5CN + 3NaCl + \tfrac{1}{2}(CN)_2 + CuCN + NH_3$$

Still greater efficiencies are stated to have been accomplished in recent German industrial practice, simply by the use of excess sodium cyanide. The following reaction was conducted at 16°C. at a pH of 7 in 75–80 per cent yields.



Furthermore, acidification of the cyanide solution after removal of the product permitted a 90 per cent recovery of cuprous cyanide (576).

In recent years the mechanism of the Sandmeyer and Gattermann reactions has been the subject of polemic discussions, the principal question being whether the diazonium halide reacts through an aryl free radical or through an entirely ionic mechanism. The non-ionic *syn-* and *anti*-diazocyanides (now thought by Hodgson (269) to have isonitrile and nitrile structures, respectively) are probably not intermediates in the preparation of nitriles, as originally assumed by Hantzsch (507). In studies on the decomposition of the diazocyanides by copper powder in non-polar solvents, Stephenson and Waters found that the reactive *syn*-compound gave only traces of the nitrile and considerable reduction to aryl and diaryl hydrocarbons. In polar solvents, such as alcohol, an equilibrium between the *syn*-diazocyanide and the diazonium salt was thought to exist. Decomposition with copper in this medium gave somewhat larger quantities of the nitrile whose precursor must have been the salt $[ArN_2]^+CN^-$ (540). In a normal diazonium halide–cuprous cyanide reaction the salt is probably in the form of a copper complex, $[ArN_2]^+[Cu(CN)_2]^-$. In the mechanism proposed by Waters, a non-ionic decomposition of the cation proceeds through the aryl free radical in the following manner (586):

$$Cu^+ + [Ar:N:::N:]^+ \rightarrow Cu^{++} + Ar\cdot + N_2$$

$$Ar\cdot + CN^- \rightarrow ArCN + e$$

$$e + Cu^{++} \rightarrow Cu^+$$

An alternative mechanism, involving ionic reactions of complex double salts of the type $[(ArN_2)Cu_2]X_3$, has been recently discussed in detail by Hodgson (269a).

Practical laboratory procedures for the synthesis of nitriles by the Sandmeyer method are given by Weygand (591) and Clarke and Reade (119). The principal variations are in the manner of preparing the fresh cuprous cyanide solution. A method of preparing dry cuprous cyanide which can be kept indefinitely and used as needed by dissolving in sodium cyanide solution has been published recently. The method also avoids loss of cyanide through evolution of cyanogen (31).

$$2CuSO_4 + 2NaCN + NaHSO_3 + H_2O \rightarrow 2CuCN + 2NaHSO_4$$

Occasionally, difficultly convertible compounds will react if the diazonium compound is added to a refluxing solution of the cyanide (17).

A few aromatic amino compounds such as *o*-aminobenzaldehyde and its derivatives (106), *o*-aminophenol (499), and 2-methyl-3-aminofuran (541) could not be converted to the nitrile by the Sandmeyer technique. However, literally hundreds of nitriles of widely varying structure have been prepared in this manner. A few selected types are listed in table 2 to illustrate the general non-interference of extraneous substituents even when in the ortho position.

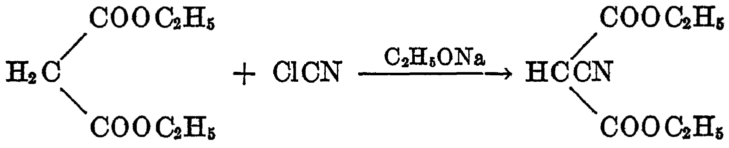
F. ORGANOMETALLIC COMPOUNDS AND CYANOGEN DERIVATIVES (GRIGNARD SYNTHESIS)

The first reaction of organometallic compounds and cyanogen derivatives was reported in 1868 by Gal, who obtained propionitrile by treating diethylzinc with cyanogen chloride (205).

$$(C_2H_5)_2Zn + 2ClCN \rightarrow 2C_2H_5CN + ZnCl_2$$

Frankland and Graham conducted a similar reaction with cyanogen in 1880 (195), and shortly afterwards Calmels extended the reaction to triethylaluminum (102). These syntheses, however, proved to be of theoretical rather than practical interest.

The reaction of cyanogen chloride with the sodium derivative of malonic ester to give ethyl cyanomalonate was reported by Haller in 1879 (236):



$$H_2C\begin{matrix}\diagup COOC_2H_5 \\ \diagdown COOC_2H_5\end{matrix} + ClCN \xrightarrow{C_2H_5ONa} HC\begin{matrix}\diagup COOC_2H_5 \\ CN \\ \diagdown COOC_2H_5\end{matrix}$$

The reaction has been extended to the synthesis of cyanoform, $CH(CN)_3$, from malononitrile (241, 516) and of ethyl α-cyano-β-ketobutyrate from acetoacetic ester (238). A more detailed study of the malonic ester reaction indicates that it may be conveniently effected by passing gaseous cyanogen chloride into a refluxing alcoholic solution of the salt. At 12–15°C., the principal products are the ester of ethylmalonic acid and sodium cyanate. The best yields (80–90 per cent) of a purer product are obtained with the dry sodium derivative and cyanogen chloride in anhydrous ether. The use of cyanogen bromide results only in

TABLE 2

Preparation of nitriles from diazonium halides

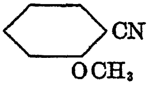
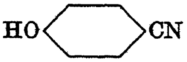
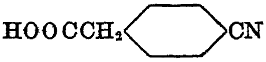
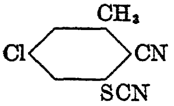
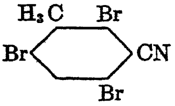
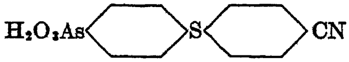
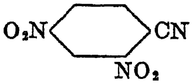
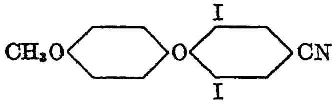
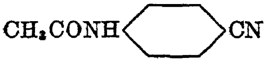
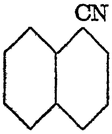
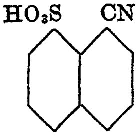
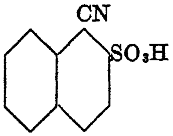
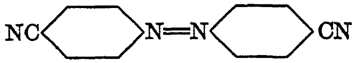
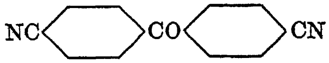
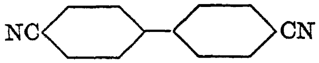
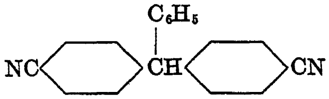
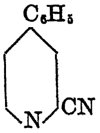
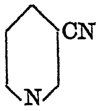
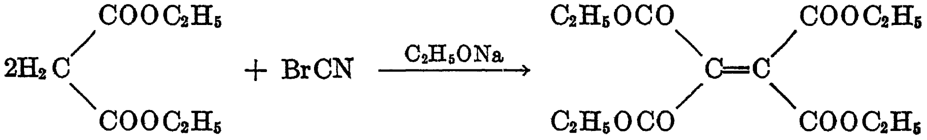
PRODUCT	YIELD	REFERENCE
	per cent	
	80	(326)
 (at 95°C.)	70	(17)
	50	(290)
	"Very good"	(262)
	48	(589)
	32	(165)
	85	(546)
		(244)
	69	(55)
	78	(499)

TABLE 2—*Concluded*

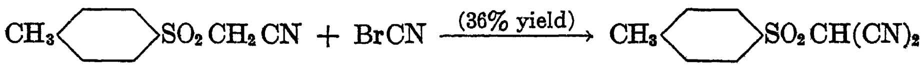
PRODUCT	YIELD	REFERENCE
	per cent	
	77	(64)
	92	(64)
	45	(17)
	68	(17)
	66	(156)
	5	(17)
		(100)
	50	(48)

the formation of tetracarbethoxyethylene, while cyanogen iodide gives the saturated analogue (402).



$$2H_2C(COOC_2H_5)_2 + BrCN \xrightarrow{C_2H_5ONa} (C_2H_5OCO)_2C{=}C(COOC_2H_5)_2$$

Cyanomethyl sulfones undergo a similar reaction (16).



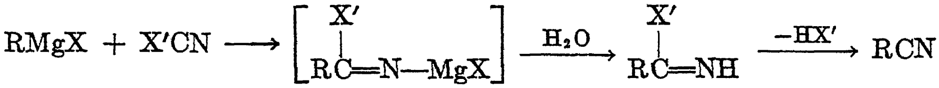
The silver salt of diethyl cyanomalonate has been converted by cyanogen chloride to the dicyanomalonate (402).

Sodium derivatives of acetylenic compounds undergo an analogous metathetical reaction. Moureu and Delange in 1901 found that sodium phenylacetylide was converted to phenylpropiolonitrile by the action of cyanogen, while cyanogen bromide gave only the bromo derivative (412).

$$C_6H_5C{\equiv}CBr \xleftarrow{BrCN} C_6H_5C{\equiv}CNa \xrightarrow{(CN)_2} C_6H_5C{\equiv}CCN$$

In 1911 Grignard applied the versatile organomagnesium reagent that bears his name to the above reactions (222). Together with his coworkers (223, 225) he found that the reaction with cyanogen halides invariably took two simultaneous courses, resulting in the formation of a halide and a nitrile. In the latter case, the mechanism is assumed to involve the same type of intermediates that have been isolated in the reaction of Grignard reagents with nitriles.

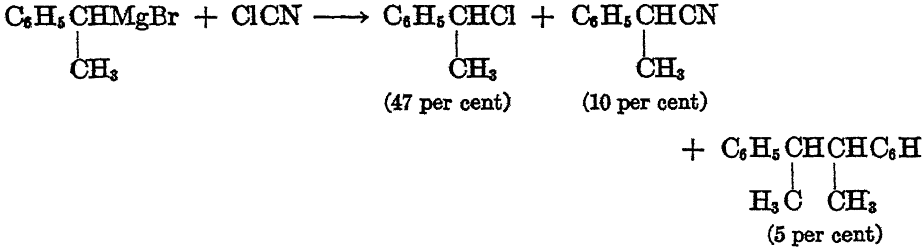
$$RMgX + X'CN \longrightarrow RX' + MgXCN$$



$$RMgX + X'CN \longrightarrow \left[\overset{X'}{R\overset{|}{C}}{=}N{-}MgX\right] \xrightarrow{H_2O} \overset{X'}{R\overset{|}{C}}{=}NH \xrightarrow{-HX'} RCN$$

With primary aliphatic, acetylenic, or aryl Grignard reagents, cyanogen chloride leads primarily to the formation of nitriles, together with minor amounts of the chlorides (226). Secondary, alicyclic, and tertiary aliphatic reagents, on the other hand, lead largely to the formation of chlorides.

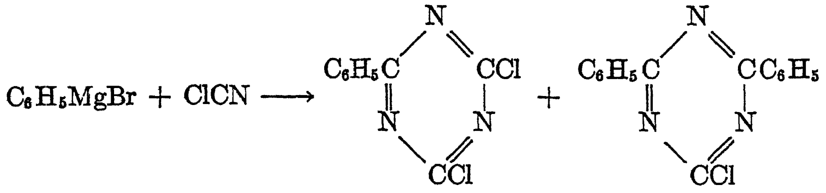
$$\underset{}{(CH_3)_2CHMgBr} + ClCN \longrightarrow \underset{(67\ \text{per cent})}{(CH_3)_2CHCl} + \underset{(9\ \text{per cent})}{(CH_3)_2CHCN}$$



$$C_6H_5\underset{CH_3}{\underset{|}{C}}HMgBr + ClCN \longrightarrow \underset{(47\ \text{per cent})}{C_6H_5\underset{CH_3}{\underset{|}{C}}HCl} + \underset{(10\ \text{per cent})}{C_6H_5\underset{CH_3}{\underset{|}{C}}HCN} + \underset{(5\ \text{per cent})}{C_6H_5\underset{H_3C}{\underset{|}{C}}H\underset{CH_3}{\underset{|}{C}}HC_6H_5}$$

$$(C_6H_5)_2CHMgBr + ClCN \longrightarrow \underset{(42\ \text{per cent})}{(C_6H_5)_2CHCl} + \underset{(8\ \text{per cent})}{(C_6H_5)_2CHCN} + \underset{(5\ \text{per cent})}{(C_6H_5)_2CHCH(C_6H_5)_2}$$

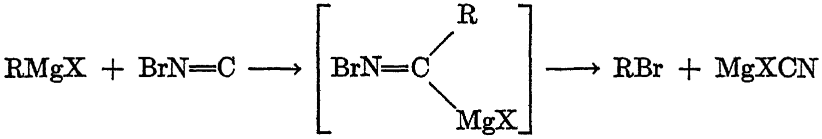
Cyanogen bromide and cyanogen iodide lead almost entirely to the organic halogen compounds with all types of reagents. This reaction, incidentally, has proven useful for the conversion of unsaturated Grignard reagents to unsaturated halides (chlorine or bromine cannot be used without addition to the olefinic linkage). By dropping the Grignard reagent into a solution of cyanogen chloride, 55–80 per cent yields of benzonitrile, α-naphthonitrile, anisonitrile, phenylpropionitrile, amylpropiolonitrile, and other similar compounds have been obtained (222, 225, 227, 228). In the presence of hydrogen chloride, the reaction leads to phenylchlorotriazines (444).



If the Grignard reagent is present in excess during the reaction, formation of a diketone will result. For example, *o*-ditolylketone was formed in yields of 70 per cent based on cyanogen chloride and over 50 per cent based on the Grignard reagent when the latter was present in excess (224).

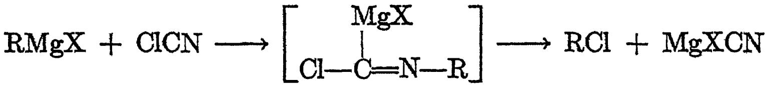
Cyanogen chloride reacts with butylmagnesium bromide to give slightly higher yields of nitrile (47 per cent) than when dibutylmagnesium is used (34 per cent) (130).

Grignard hypothesized that the difference between the behavior of cyanogen chloride and that of cyanogen bromide or iodide was due to the predominant existence of the latter two compounds in the isocyanide form, C═N—X (223).



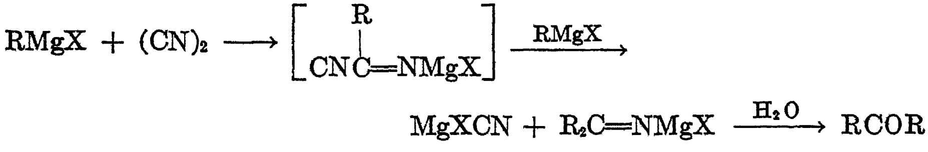
The difference between the action of primary and of tertiary reagents was more vaguely explained on the basis of a preferred "affinity" of a tertiary radical for the halogen.

It is known, however, that certain tertiary alcohols and their derivatives will add to organic nitriles in an abnormal fashion, with the resultant formation of *N*-substituted amides, while primary alcohols lead in the normal fashion to imino ethers and esters. It seems more probable, therefore, that a tertiary Grignard reagent would add in abnormal fashion to cyanogen chloride to produce an intermediate of the following type:



$$\mathrm{RMgX} + \mathrm{ClCN} \longrightarrow \left[\mathrm{Cl{-}\overset{\overset{\displaystyle MgX}{|}}{C}{=}N{-}R}\right] \longrightarrow \mathrm{RCl} + \mathrm{MgXCN}$$

In view of the limitations of the reaction with cyanogen halides, it was natural to turn to the use of cyanogen. Blaise had used these reagents in 1901 but the sole products obtained were ketones (50).

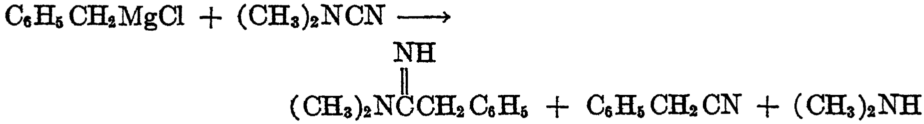


$$\mathrm{RMgX} + (\mathrm{CN})_2 \longrightarrow \left[\mathrm{CN\overset{\overset{\displaystyle R}{|}}{C}{=}NMgX}\right] \xrightarrow{\mathrm{RMgX}}$$

$$\mathrm{MgXCN} + \mathrm{R_2C{=}NMgX} \xrightarrow{\mathrm{H_2O}} \mathrm{RCOR}$$

However, by using the above-mentioned technique of keeping the cyanogen in excess, Grignard was able to obtain the nitriles as products (222, 223, 224). The yields were not quite as good as those obtained with cyanogen chloride for primary aliphatic and aromatic Grignard reagents. However, secondary and alicyclic reagents were found to give nitriles in 30–60 per cent yields. This technique is especially valuable, since nitriles of this type are not easily obtained in good yield by other direct syntheses.

Dimethyl cyanamide has been reported to react with benzylmagnesium chloride to give phenylacetonitrile in addition to the normal amidine, but only the latter is obtained from benzylmagnesium bromide (579).



$$C_6H_5CH_2MgCl + (CH_3)_2NCN \longrightarrow (CH_3)_2N\overset{\overset{\displaystyle NH}{\|}}{C}CH_2C_6H_5 + C_6H_5CH_2CN + (CH_3)_2NH$$

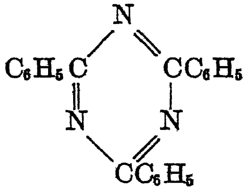
III. Cyanogenation of Aromatic Compounds

A. THE FRIEDEL–CRAFTS–KARRER SYNTHESIS

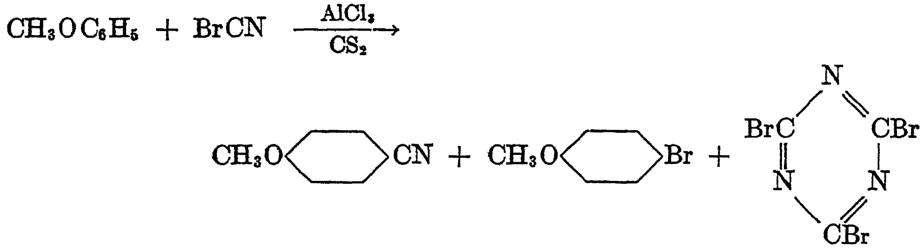
Friedel and Crafts in 1878 extended their technique of acetylation of aromatic hydrocarbons with anhydrous aluminum chloride catalysts to include cyanogen chloride as a reagent (198).

$$C_6H_6 + ClCN \xrightarrow{AlCl_3} C_6H_5CN + HCl$$

In their hands, the yield of benzonitrile was very poor and considerable amounts of high-boiling complex by-products were formed. A little later Scholl and Nörr studied the reaction of cyanogen bromide and benzene in carbon bisulfide solution and found that the principal product was the trimer of benzonitrile, *sym*-triphenyltriazine or cyaphenin (519).

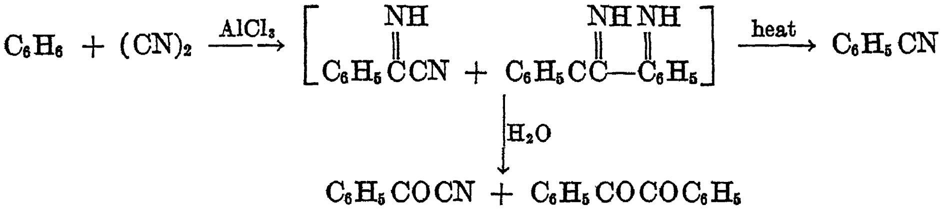


When the reaction was extended to more reactive compounds such as anisole, only 4 per cent of *p*-methoxybenzonitrile was formed together with some trimer, about 30 per cent of *p*-bromoanisole, and some cyanuryl bromide.



Further investigation revealed that benzonitrile was obtained when benzene was treated with mercuric fulminate and anhydrous aluminum chloride, whereas the use of hydrated aluminum chloride yielded benzaldehyde oxime (518).

Degrez, working in Friedel's laboratory, observed that the use of cyanogen in place of cyanogen chloride gave rise to benzonitrile upon distillation of the reaction complex (152). When the reaction complex was hydrolyzed with dilute acids, however, it was found that benzoyl cyanide was the principal product, some benzil being obtained also (578).

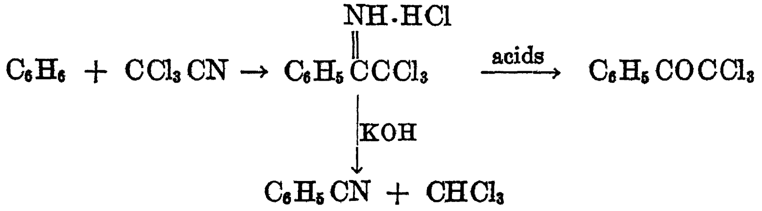


$$\begin{array}{c} C_6H_6 + (CN)_2 \xrightarrow{AlCl_3} \left[C_6H_5\overset{NH}{\overset{\|}{C}}CN + C_6H_5\overset{NH}{\overset{\|}{C}}\overset{NH}{\overset{\|}{C}}-C_6H_5 \right] \xrightarrow{heat} C_6H_5CN \\ \downarrow{\scriptstyle H_2O} \\ C_6H_5COCN + C_6H_5COCOC_6H_5 \end{array}$$

The value of the Friedel–Crafts synthesis as a preparative method did not become apparent until Karrer examined the reaction in 1919 (303, 304). His technique differed from that of earlier workers only in that finely ground aluminum chloride and freshly prepared cyanogen bromide were employed. These simple precautions led to the preparation of benzonitrile in 69 per cent yield, whereas three-week-old cyanogen bromide led exclusively to the formation of the trimeric form. Phenol ethers gave even better yields. The reaction is also applicable to hydrocarbons such as toluene, acenaphthene, and anthracene. Phenanthrene, however, is unreactive (408). Thiophene is converted to the α-cyano derivative, but if both α-positions are occupied, the β-nitrile is formed (300). Furan does not undergo the reaction in satisfactory yield (312). A certain amount of the aryl bromide is formed as a by-product in all of these reactions (32). Cyanogen chloride may be used with equally satisfactory results, but cyanogen iodide is partially degraded to free iodine.

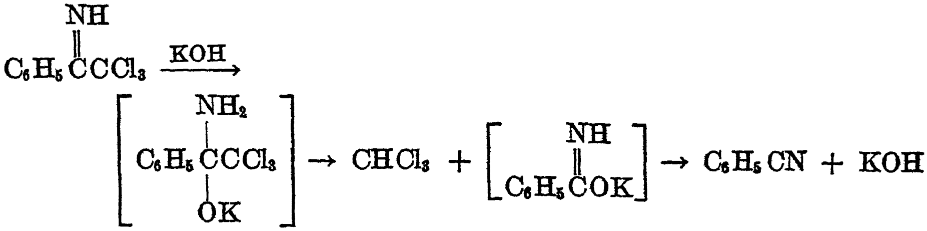
B. THE HOUBEN–FISCHER SYNTHESIS

An extremely facile method for the preparation of aromatic nitriles was introduced by Houben and Fischer in 1929 (277). These authors, while investigating the formation of aryl ketones from nitriles, noted that trichloroacetonitrile led to the expected intermediate, the ketimine hydrochloride. This intermediate was hydrolyzed by dilute acids in the normal fashion to the trichloromethyl aryl ketone, but treatment with potassium hydroxide led to the aromatic nitrile in excellent yield.



$$\begin{array}{c} C_6H_6 + CCl_3CN \rightarrow C_6H_5\overset{NH\cdot HCl}{\overset{\|}{C}}CCl_3 \xrightarrow{acids} C_6H_5COCCl_3 \\ \downarrow{\scriptstyle KOH} \\ C_6H_5CN + CHCl_3 \end{array}$$

Houben has stated that the alkali acts catalytically by the following mechanism, which involves the potassium salt of the pseudo amide as an intermediate:



$$C_6H_5\overset{NH}{\overset{\|}{C}}CCl_3 \xrightarrow{KOH} \left[C_6H_5\underset{OK}{\overset{NH_2}{C}}CCl_3\right] \rightarrow CHCl_3 + \left[C_6H_5\overset{NH}{\overset{\|}{C}}OK\right] \rightarrow C_6H_5CN + KOH$$

Trichloroacetonitrile appears to be a highly specific reagent, as alkaline hydrolysis of the ketimines from dichloroacetonitrile and chloroacetonitrile leads only to the ketone. The conditions and catalysts needed for formation of the intermediate ketimine depend on the reactivity of the aromatic compound. Phenols and their ethers require only dry hydrogen chloride, while the more inert hydrocarbons require the addition of the chlorides of zinc or aluminum. The intermediate ketimine need not be isolated, and the use of ammonia gas in the degradation step inhibits ketone formation and gives improved yields.

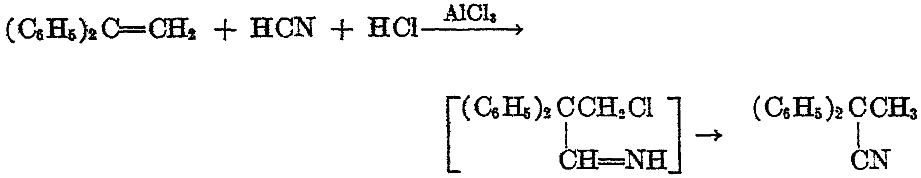
Since the —CCl_3 group commonly behaves as a pseudo-halogen, the over-all reaction resembles the Friedel–Crafts synthesis. More widespread adoption of this method as a synthetic technique is probably dependent upon the future availability of trichloroacetonitrile.

The products and yields obtained from some typical aromatic compounds and trichloroacetonitrile are listed in table 3 (277).

IV. ADDITION OF HYDROGEN CYANIDE

A. ADDITION OF HYDROGEN CYANIDE TO OLEFINIC AND ACETYLENIC COMPOUNDS

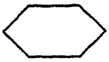
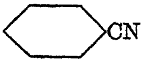
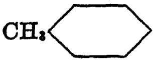
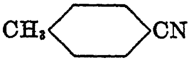
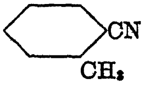
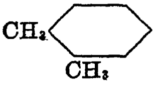
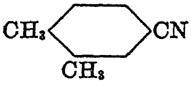
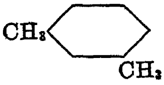
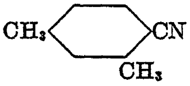
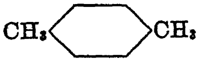
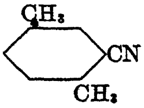
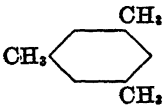
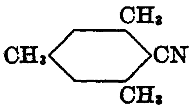
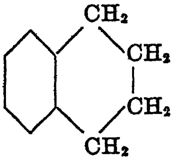
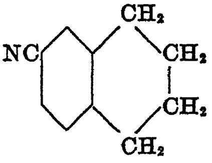
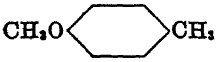
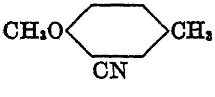
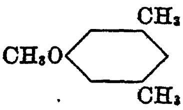
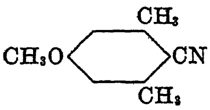
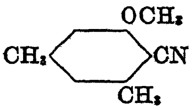
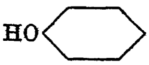
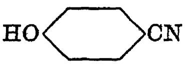
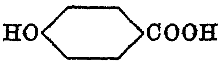
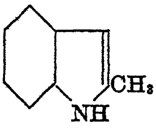
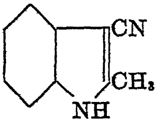
The addition of hydrogen cyanide to simple olefins does not take place satisfactorily, although propionitrile has been isolated by passing ethylene and hydrogen cyanide through an ozonizer or silent electric discharge (104). Recent patents describe the formation in low yields of higher homologues at 250–350°C. and 10–100 atm. pressure in the presence of metal catalysts (557). Trimethylacetonitrile is obtained in 46 per cent yield from isobutylene and hydrogen cyanide at 350–400°C. over alumina gel (244a). The highly reactive diolefin, allene, is reported to add hydrogen cyanide at 425°C. over a zinc oxide catalyst to give 20 per cent conversion and 55 per cent yields of a mixture of nitriles consisting predominantly of methacrylonitrile and lesser amounts of *cis*- and *trans*-crotononitriles (99). The use of aluminum chloride catalyst enabled Wieland and Dorrer to cause 1,1-diphenylethylene to add hydrogen cyanide. Considerable dimerization and reduction of the hydrocarbon occurred concurrently. The chloroaldimine was hypothesized as the intermediate.



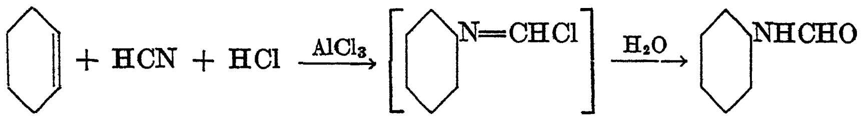
$$(C_6H_5)_2C{=}CH_2 + HCN + HCl \xrightarrow{AlCl_3} \left[(C_6H_5)_2\underset{CH{=}NH}{C}CH_2Cl\right] \rightarrow (C_6H_5)_2\underset{CN}{C}CH_3$$

TABLE 3

Nitriles prepared with trichloroacetonitrile

REAGENT	PRODUCTS AND YIELDS
	 (69%)
	 (68%) +  (15%)
	 (86%)
	 (87%)
	 (82%)
	 (68%)
	 (65%) and some α-isomer
	 (67%)
	 (89%) +  (some)
	 (25%) + 
	 (95%)

Under similar conditions, stilbene gave low yields of an unidentified basic compound, while cyclohexene added hydrogen cyanide in an abnormal fashion to give a 30 per cent yield of *N*-cyclohexylformamide (598).



Butadiene also reacts with hydrogen cyanide under the influence of a strong acidic catalyst such as boron trifluoride, but the structures of the products have not been elucidated (129). A recent patent describes the formation of 3-pentenonitrile in 21 per cent yield from butadiene and hydrogen cyanide at 90–100°C. in an aqueous acidic ammonium chloride–cuprous chloride solution.

$$CH_2{=}CHCH{=}CH_2 + HCN \rightarrow CH_3CH{=}CHCH_2CN$$

Isoprene and cyclopentadiene react similarly (523a).

The addition of hydrogen cyanide to acetylene was observed in 1911 when a 5 per cent yield of succinic acid was formed from a mixture of calcium carbide, potassium cyanide, and dilute sulfuric acid (132). Although a purely thermal vapor-phase reaction of acetylene and hydrogen cyanide leads to a complex mixture of bases including pyrrole, pyridine, aniline, and quinoline (396), succinonitrile and some acrylonitrile are obtained in about 60 per cent yield at 355°C. over cadmium and magnesium oxide catalysts (104).

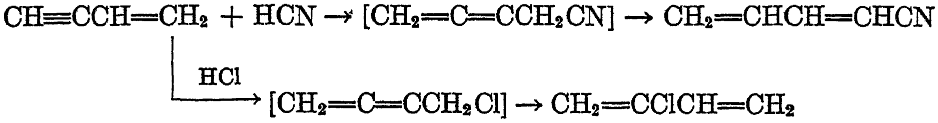
$$CH{\equiv}CH + HCN \rightarrow CH_2{=}CHCN \xrightarrow{HCN} CNCH_2CH_2CN$$

An early development in the vapor-phase process included the use of alkali or alkaline earth catalysts at 400–500°C., a procedure which enabled the intermediate acrylonitrile to be isolated in about 10 per cent yield (35). It has been demonstrated recently that these conditions actually produce acrylonitrile in much higher yields and that the low recovery of product was caused by secondary reactions promoted by basic by-products. Thus 70 per cent yields are obtained by condensing the product gases in acetic acid or monosodium hydrogen phosphate solution (170). Similar yields of acrylonitrile are stated to be obtained when the oxides of zinc, cadmium, or magnesium are employed as catalysts (535). A novel process involves the simultaneous reaction of ammonia and methane to form acetylene and hydrogen cyanide. The latter two compounds then combine to give acrylonitrile (171).

The most satisfactory reaction conditions involve the use of a Nieuwland-type catalyst,—a concentrated aqueous solution of cuprous chloride and ammonium chloride (346, 503). This process has been operated very successfully in commercial production and about 25,000,000 pounds of acrylonitrile were reported to have been produced in Germany in 1944. Acetylene and hydrogen cyanide in a 10:1 ratio are passed through a rubber-lined catalyst chamber containing a liquid mixture of cuprous chloride (65 parts), ammonium chloride (35 parts), concentrated hydrochloric acid (2 parts) in water (56 parts) held at 70–90°C.

Yields of acrylonitrile of 80–95 per cent based on hydrogen cyanide are obtained. By-products include 4 per cent acetaldehyde, 1 per cent chloroprene, 4 per cent 1-cyanobutadiene, 2 per cent lactonitrile, and traces of acetylene polymers (103, 247).

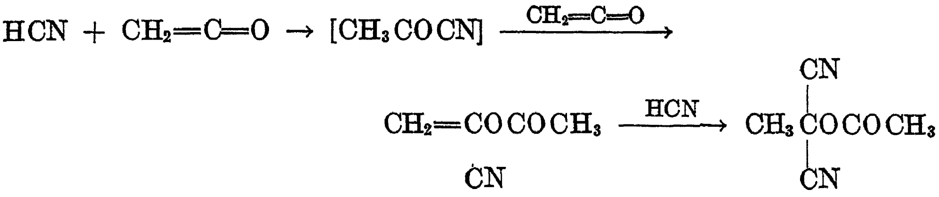
The addition of hydrogen cyanide to vinylacetylene proceeds by a 1,4-addition mechanism, the intermediate undergoing a prototropic rearrangement to 1-cyanobutadiene. This is in contrast to the 1,4-addition of hydrogen chloride, followed by an anionotropic rearrangement resulting in 2-chlorobutadiene (127).



$$CH{\equiv}CCH{=}CH_2 + HCN \rightarrow [CH_2{=}C{=}CCH_2CN] \rightarrow CH_2{=}CHCH{=}CHCN$$

$$\xrightarrow{HCl} [CH_2{=}C{=}CCH_2Cl] \rightarrow CH_2{=}CClCH{=}CH_2$$

The addition of hydrogen cyanide to ketene was first reported by Deakin and Wilsmore in 1910 (150), although later investigators were unable to duplicate the results (283). Further study of the reaction has indicated that alkaline catalysts and relatively low temperatures are required. A by-product, acetyl cyanide dimer, is also obtained.



$$HCN + CH_2{=}C{=}O \rightarrow [CH_3COCN] \xrightarrow{CH_2=C=O} CH_2{=}\underset{CN}{C}OCOCH_3 \xrightarrow{HCN} CH_3\overset{CN}{\underset{CN}{C}}OCOCH_3$$

The reaction is best carried out in a solvent at −50°C. to 30°C. in the presence of a tertiary amine or alkali metal acetate. A variation in yields of 8–82 per cent for α-cyanovinyl acetate and 5–72 per cent for acetyl cyanide dimer are obtained, depending on the conditions of the reaction. High yields of the first product are favored by acetic anhydride as a solvent and low reaction temperatures (299, 350, 577). The structure of acetyl cyanide dimer, which had been previously prepared from potassium cyanide and acetic anhydride or from monomeric pyruvonitrile by the catalytic action of sodium, has been established by hydrolysis to isomalic acid (86, 350). The intermediate pyruvonitrile is obtained by reaction in the vapor phase at 200–400°C. (476).

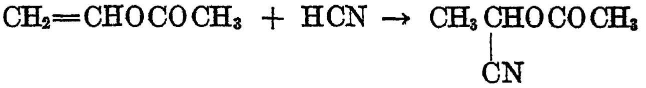
Diphenylketene fails to give an adduct with hydrogen cyanide in ether or in pressure tubes, but the effect of alkaline catalysts apparently has not been investigated (219).

An olefinic double bond is made highly susceptible to hydrogen cyanide addition by an alkoxy or acyloxy substituent. Thus, vinyl ethers of methyl, ethyl, butyl, and octadecyl alcohols are reported to add hydrogen cyanide in good yield in pyridine solution at 100–150°C. (34).

$$CH_2{=}CHOR + HCN \rightarrow CH_3CH(OR)CN$$

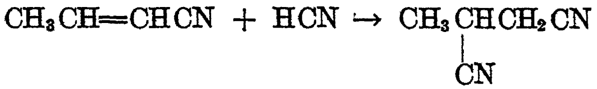
The use of stronger bases or primary and secondary amines results in poorer yields.

Vinyl acetate and related compounds react similarly at lower temperatures (25–60°C.) in the presence of tertiary amine or alkali metal cyanide catalysts. The exothermic reaction (25.5 kg.-cal. per mole) is promoted by the presence of acetaldehyde and gives 90–95 per cent yields (174, 239, 344).



$$CH_2{=}CHOCOCH_3 + HCN \rightarrow CH_3\underset{\underset{CN}{|}}{C}HOCOCH_3$$

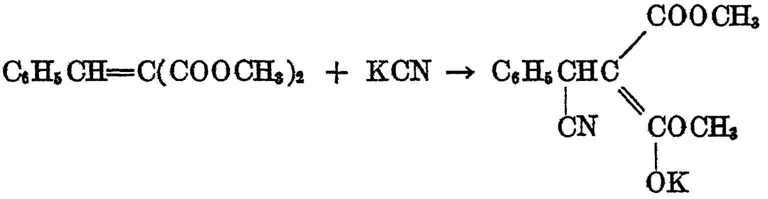
The addition of hydrogen cyanide to the double bond of an α,β-unsaturated acid or its derivatives proceeds very readily. The addition of hydrogen cyanide to crotononitrile was observed by Claus in 1878 (120).



$$CH_3CH{=}CHCN + HCN \rightarrow CH_3\underset{\underset{CN}{|}}{C}HCH_2CN$$

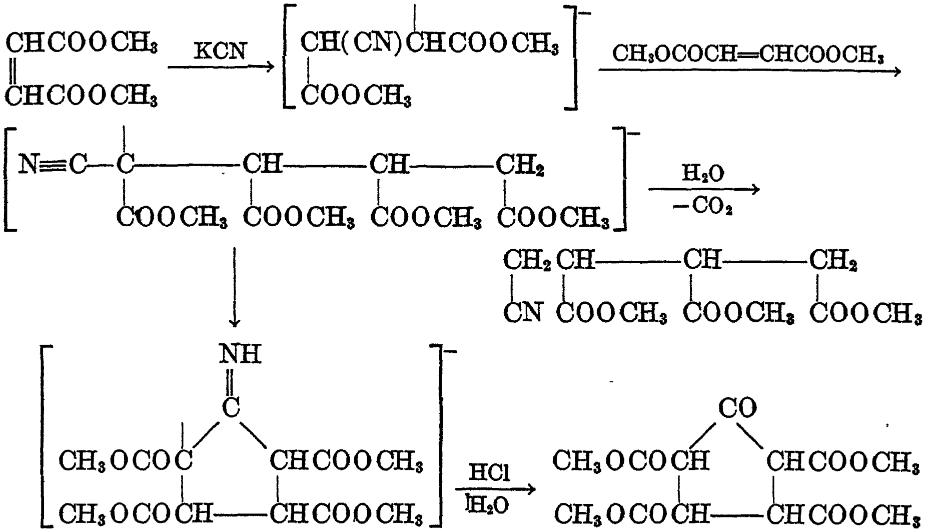
In 1903, Lapworth demonstrated that the reaction required basic catalysis; under these conditions he developed a method which has become a very useful synthesis for a large variety of succinic acid derivatives (265, 352, 354).

In absolute methanol as solvent Michael and Weiner have isolated the potassium salt of the adduct derived from benzalmalonic ester, although they failed to recognize the ionic nature of the reaction (399).

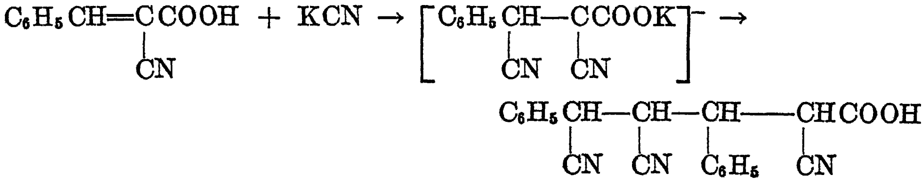


The mechanism has been shown by Ingold and coworkers to be initiated by attack of the cyanide ion at the β-carbon (essentially a 1,4-addition to the conjugated C═C—C═O system). As such it is entirely analogous to the Michael addition of alkali salts of malonic esters. It differs from additions of compounds like hydrogen bromide in that hydrogen cyanide acts as a nucleophilic reagent. The cyanide ion is strongly attracted to the β-carbon atom of the double bond because of the greatly decreased electron density at that location. This situation is due to electron withdrawal and polarization toward the α-carbon under the influence of the carbonyl group (53, 98, 168).

In general, additions proceed with greater ease and in higher yield if the reacting acrylic acid, ester, or nitrile is substituted in the α-position by another negative group (carbalkoxy, cyano, or phenyl), while the accumulation of substituents in the β-position lowers the yield (168, 265, 399). The presence of a negative substituent in the β-position favors the occurrence of side-reactions. Thus, from potassium cyanide and methyl fumarate is obtained an intermediate which undergoes a Michael-type addition to a second molecule of fumaric ester. This product is either partially saponified and decarboxylated if water is present or undergoes a Dieckmann condensation with the formation of a cyclopentanone derivative in absolute methanol (399).

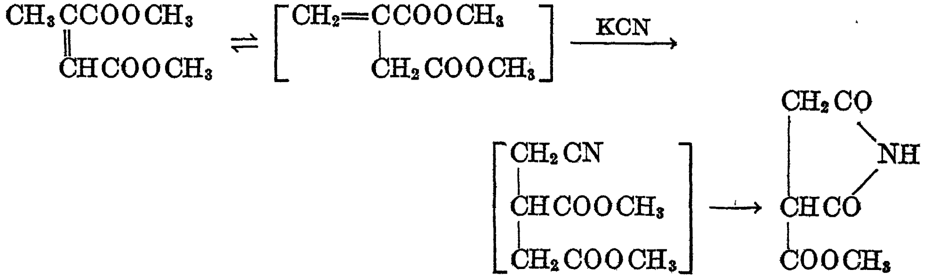


α-Cyanocinnamic acid is converted by a similar mechanism to 3,5-diphenyl-2,4,5-tricyanovaleric acid (560).

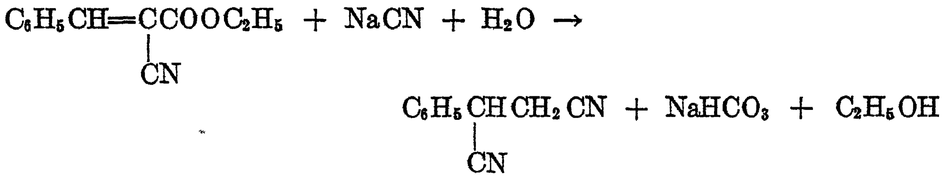


$$C_6H_5CH{=}\underset{CN}{C}COOH + KCN \rightarrow \left[C_6H_5\underset{CN}{CH}-\underset{CN}{C}COOK\right]^- \rightarrow C_6H_5\underset{CN}{CH}-\underset{CN}{CH}-\underset{C_6H_5}{CH}-\underset{CN}{CH}COOH$$

Ethyl itaconate quantitatively forms the expected cyanomethylsuccinic ester (275). However, methyl citraconate apparently isomerizes to the itaconic ester before addition. The final product is the methyl ester-imide of tricarballylic acid (399).

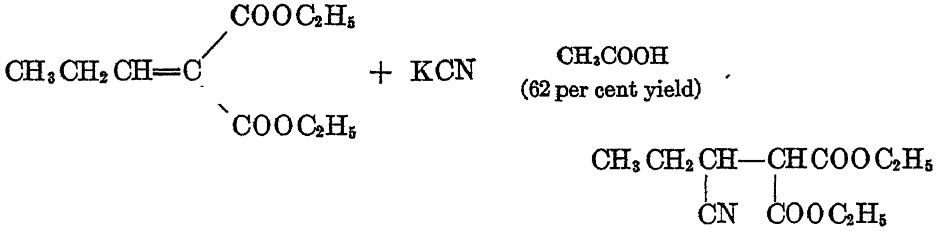


The basicity of the reaction is increased by the formation of alkali hydroxides. If carried out in the presence of water this usually results in at least partial saponification of an ester or nitrile group. Decarboxylation frequently follows, as in the preparation of phenylsuccinonitrile from ethyl α-cyanocinnamate (415).



$$C_6H_5CH{=}\underset{\displaystyle CN}{\underset{|}{C}}COOC_2H_5 + NaCN + H_2O \rightarrow C_6H_5\underset{\displaystyle CN}{\underset{|}{CH}}CH_2CN + NaHCO_3 + C_2H_5OH$$

This hydrolysis and decarboxylation may be diminished by the presence of acetic acid (614).

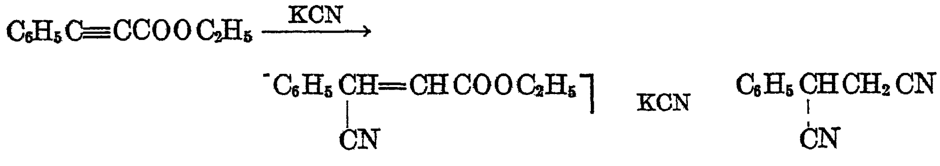


The alkali may also induce cleavage of a formyl group, as in the quantitative conversion of the half-aldehyde of maleic acid to succinic acid (179).

$$CHOCH{=}CHCOONa \xrightarrow{KCN} HOOCCH_2CH_2COOH + HCOOH$$

2-Cyano-3,4-diphenyl-4-crotonolactone is reported to be inert toward hydrogen cyanide addition (376).

α,β-Triple-bonded compounds such as phenylpropiolic esters add two molecules of hydrogen cyanide with concurrent saponification of the ester group and decarboxylation. The intermediate α-cyanocinnamate was not isolated, but phenyl succinonitrile was obtained in 20 per cent yield (124, 399).

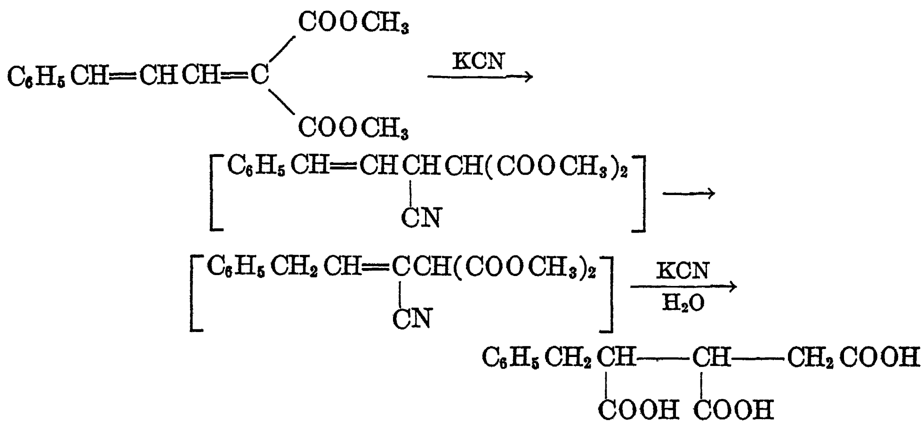


$$C_6H_5C{\equiv}CCOOC_2H_5 \xrightarrow{KCN} \left[C_6H_5\underset{\displaystyle CN}{\underset{|}{CH}}{=}CHCOOC_2H_5\right] \xrightarrow{KCN} C_6H_5\underset{\displaystyle CN}{\underset{|}{CH}}CH_2CN$$

The intermediate mononitrile has been isolated in fair yield from methyl propiolate (343).

$$CH{\equiv}CCOOCH_3 + HCN \rightarrow CNCH{=}CHCOOCH_3$$

Cinnamalmalonic ester reacts with 1 mole of potassium cyanide, with the ultimate formation of styrylsuccinic acid, an α,β-addition (560). The tricarboxylic acid obtained by use of an excess of cyanide was shown to be 4-phenyl-1,2,3-butanetricarboxylic acid, which resulted from two such α,β-additions made possible by an intermediate prototropic shift of the double bond (168).

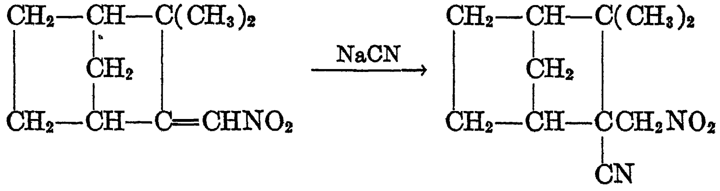


In the absence of water the predominant product is one formed by a Michael addition of the first intermediate to unchanged cinnamylidenemalonic ester (399).

The presence of an acid or ester group is not essential for the success of this addition, since α,β-unsaturated nitriles, sulfones, or nitro compounds react with equal facility. For example, acrylonitrile is converted by the action of sodium cyanide in aqueous solution at 80°C. to succinimide in 70 per cent yield (614), while the use of anhydrous hydrogen cyanide in the presence of 1–3 per cent of sodium cyanide at 30–50°C. leads to succinonitrile in 95 per cent yield (385a, 530a). Alkylidenemalononitriles yield saturated trinitriles in excellent yield (134).

$$RCH{=}C(CN)_2 \xrightarrow{KCN} RCH(CN)CH(CN)_2$$

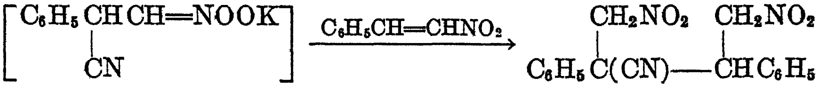
Reactions of this type are reversed at high temperatures (477). Nitrocamphene is converted by alcoholic sodium cyanide to nitroisocamphanyl cyanide (366).



Buckley has shown recently that the lower nitroölefins react similarly in yields ranging from 15 to 90 per cent (96a).

β-Nitrostyrene reacts with potassium cyanide, but the intermediate compound apparently undergoes a condensation of the Michael type with a second molecule of the nitroölefin. The structure of the resultant product, 2,3-diphenyl-2-cyano-1,4-dinitrobutane, was established by degradation to α,β-diphenylsuccinic acid (274).

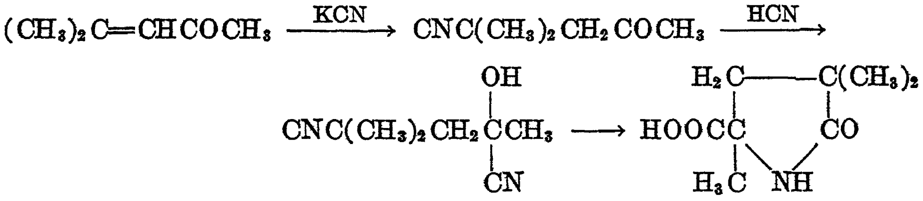
$$C_6H_5CH{=}CHNO_2 + KCN \rightarrow$$



$$\left[C_6H_5\underset{\displaystyle CN}{\underset{|}{C}}H\,CH{=}NOOK\right] \xrightarrow{C_6H_5CH=CHNO_2} C_6H_5\overset{\displaystyle CH_2NO_2}{\overset{|}{C}}(CN)-\overset{\displaystyle CH_2NO_2}{\overset{|}{C}}HC_6H_5$$

Vinyl sulfones are converted by the same reagent to the β-cyanoethyl sulfones (345).

The reaction of alkali cyanides with a large number of α,β-unsaturated ketones has been investigated. Thus, mesityl oxide and phorone are converted in excellent yield to the ketonitrile and the ketodinitrile, respectively. In the first case, the presence of both potassium cyanide and hydrogen cyanide causes the intermediate ketonitrile to be further converted to its cyanohydrin. This is easily hydrolyzed at higher temperatures to the lactam of mesitylic acid (352).

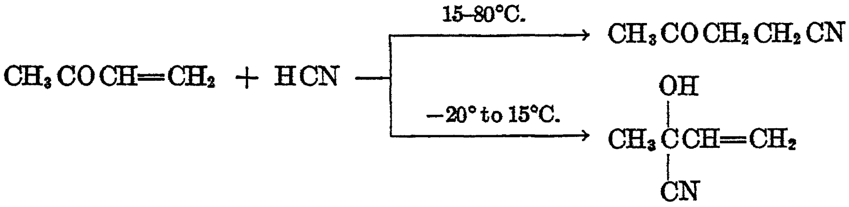


$$(CH_3)_2C{=}CHCOCH_3 \xrightarrow{KCN} CNC(CH_3)_2CH_2COCH_3 \xrightarrow{HCN}$$

$$CNC(CH_3)_2CH_2\overset{OH}{\underset{CN}{C}}CH_3 \longrightarrow$$

α-Alkylideneacetoacetic esters similarly form monolactones of tricarboxylic acids (280).

In the case of methyl vinyl ketone it is stated that the course of the addition depends largely upon the experimental conditions. At 15–80°C. the predominant reaction product is levulinonitrile, while at −20°C. to 15°C. in the presence of a diluent the cyanohydrin of methyl vinyl ketone is formed (358).

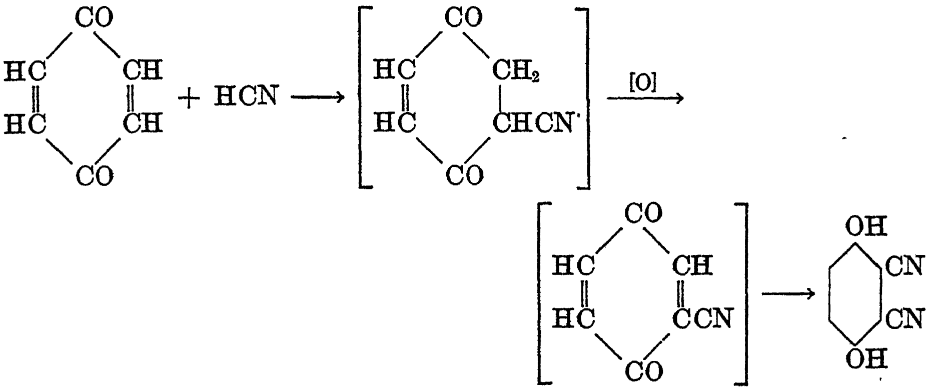


$$CH_3COCH{=}CH_2 + HCN \xrightarrow{15\text{–}80°C.} CH_3COCH_2CH_2CN$$

$$CH_3COCH{=}CH_2 + HCN \xrightarrow{-20° \text{ to } 15°C.} CH_3\overset{OH}{\underset{CN}{C}}CH{=}CH_2$$

Since aldehydes react more rapidly and completely with hydrogen cyanide than do ketones, cyanohydrin formation is the exclusive reaction with α,β-unsaturated aldehydes (399, 474). Benzalacetophenone is converted in aqueous alcohol to α-cyanobenzylacetophenone in 95 per cent yield (280), but in absolute methanol the chief products are complex cyclic compounds of incompletely elucidated structures which arise through Michael condensations of the intermediate salt and a second mole of unsaturated ketone (399). The p,p′-dimethoxychalcones, however, are reported to be completely unreactive toward potassium cyanide (142).

Two moles of hydrogen cyanide are added to quinone with the formation of 2,3-dicyanohydroquinone. Part of the quinone is simultaneously converted to hydroquinone while oxidizing the first of the unisolated mononitrile intermediates. The absence of 2,5-dicyanohydroquinone in the product is explained by the strong activating influence of the nitrile group in the second intermediate (9).



Although earlier investigators were unable to effect the addition of cyanogen halides to olefins, it has recently been demonstrated that cyanogen chloride will add to acetylene to give β-chloroacrylonitrile in good yields. An acidified aqueous cuprous ammonium chloride solution is used as the catalyst (172a).

$$ClCN + CH{\equiv}CH \rightarrow ClCH{=}CHCN$$

B. ADDITION OF HYDROGEN CYANIDE TO ALDEHYDES AND KETONES

Synthetic mandelonitrile has been known since 1832, when it was prepared from benzaldehyde and hydrogen cyanide by Winkler (602). In 1867 Gautier and Simpson isolated the first aliphatic cyanohydrin, lactonitrile, by allowing acetaldehyde to stand for several days with hydrogen cyanide (211). The method was adapted with erratic results for the preparation of other aldehyde cyanohydrins, but attempted preparations of ketone cyanohydrins were unsuccessful. Urech observed in 1872 that the latter could be formed when equivalent quantities of ketone and alkali cyanide were acidified with acetic or hydrochloric acid (571). Kiliani later noted the catalytic influence of ammonia in preparing carbohydrate cyanohydrins (310). However, it was not until 1903 that Lapworth showed that the rate of reaction was proportional to the concentration of the cyanide ion and that alkali or ammonium cyanides were the active catalysts in the modifications of Urech and Kiliani (352).

Urech's method is still popular because of its simplicity and gives a 77–78 per cent yield in the case of acetone cyanohydrin (136).

Ultee's method involves the addition of anhydrous hydrogen cyanide to the aldehyde or ketone containing a trace of alkali cyanide at about 0°C. Equilibrium is rapidly established under these conditions, and the product is then stabilized by acidification before distillation or recrystallization. Low temperatures favor high conversion (less dissociation of the cyanohydrin). The method is highly successful for most aldehydes and ketones (284, 570), and simplifies the isolation and purification of the cyanohydrin, since water and inorganic salts are present only in trace amounts. In large-scale runs, a little crude product from a previous run is stated to prevent an induction period which may be dangerous because of the highly exothermic nature of the reaction (164).

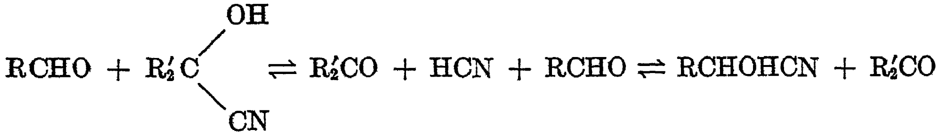
Another procedure which is a very convenient laboratory method is the sodium bisulfite modification of Pape (450).

$$RCHO + NaHSO_3 \longrightarrow RCHOHSO_3Na \xrightarrow{NaCN} RCHOHCN + Na_2SO_3$$

Several advantages are claimed for this technique. Hydrogen cyanide fumes are largely avoided since the reaction is always basic. Benzoin formation is minimized in the case of aromatic aldehydes, although some *N*-benzylidenemandelamide by-product has been isolated in the preparation of mandelonitrile (521). Very pure cyanohydrins are obtained directly if the crystalline intermediate bisulfite addition compound is washed with alcohol and benzene to remove the carbonyl compound and dried *in vacuo* to remove sulfur dioxide before treatment with a cold saturated solution of alkali cyanide (47). This technique cannot be used for a number of ketones which react with hydrogen cyanide but not with sodium bisulfite. A slight modification of the bisulfite method employs sulfurous acid (4).

The procedure of Albert, in which the aldehyde is dissolved in a water-immiscible solvent and shaken with a mixture of ammonium chloride and an alkali cyanide, is reported to be advantageous for certain aldehydes (4, 111). For example, *o*-nitrobenzaldehyde is converted to the cyanohydrin without the usual formation of tarry by-products. Curiously, the Zelinsky–Stadnikoff formation of aminonitriles does not take place in this two-phase system (see page 237).

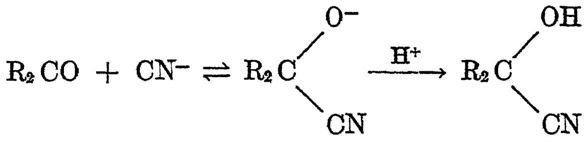
An advantageous method for the preparation of lower water-soluble cyanohydrins involves an interchange between a ketone cyanohydrin and an aldehyde. The equilibrium, which is quickly obtained in the presence of a trace of alkali, favors relatively high conversions to the aldehyde cyanohydrin.



$$RCHO + R'_2C\begin{matrix} \diagup OH \\ \diagdown CN \end{matrix} \rightleftharpoons R'_2CO + HCN + RCHO \rightleftharpoons RCHOHCN + R'_2CO$$

This procedure avoids the handling of anhydrous hydrogen cyanide and simplifies the isolation procedure by eliminating aqueous solutions of inorganic salts. The preparation of glycolonitrile, which has a particularly unfavorable distribution coefficient for extraction from aqueous solution by immiscible organic solvents, is obtained from methyl ethyl ketone cyanohydrin and formalin in 70–83 per cent yields (341, 414).

Lapworth's reaction mechanism for cyanohydrin formation (352) involves the attack of the nucleophilic cyanide ion at the point of lowest electron density, which is the carbonyl carbon atom. The intermediate then absorbs a proton from the solution.



$$R_2CO + CN^- \rightleftharpoons R_2C\begin{matrix} \diagup O^- \\ \diagdown CN \end{matrix} \xrightarrow{H^+} R_2C\begin{matrix} \diagup OH \\ \diagdown CN \end{matrix}$$

The first step is bimolecular and the rate-determining reaction, since the over-all reaction velocity is independent of hydrogen-ion concentration (3). Stewart's study of the formation and behavior of cyanohydrins in non-polar solvents has indicated that the reaction can also proceed by a non-ionic mechanism. Under these conditions a cyanohydrin–amine complex is thought to be the active catalyst (361, 542).

TABLE 4

Dissociation constants and thermodynamic stability of cyanohydrins

BENZALDEHYDES RC_6H_4CHO R =	$K \times 10^2$	ΔF
		kg.-cal.
H (99%)	0.47	−3.1
o-Nitro	0.07	−4.2
m-Nitro	0.27	−3.4
p-Nitro	1.81	−2.3
o-Chloro	0.10	−4.0
m-Chloro	0.25	−3.5
p-Chloro	0.49	−3.1
o-Methoxy	0.26	−3.5
m-Methoxy (97%)	0.43	−3.2
p-Methoxy	3.12	−2.0
o-Hydroxy	1.67	−2.4
m-Hydroxy	0.48	−3.1
p-Hydroxy	7.66	−1.5
m-Methyl	0.60	−3.0
p-Methyl	1.03	−2.7
p-Dimethylamino	39.00	−0.5

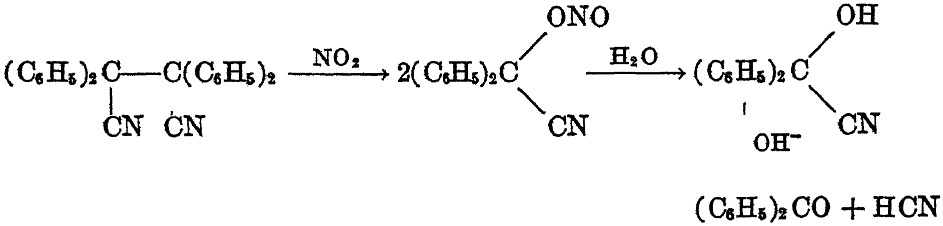
METHYL KETONES CH_3COR R =	$K \times 10^2$	ΔF
Methyl (97%)	3.05	−2.0
Ethyl	2.65	−2.1
n-Propyl	3.55	−1.9
n-Butyl	3.20	−2.0
Isopropyl	1.55	−2.4
tert-Butyl	3.10	−2.0
Benzyl	2.15	−2.2
β-Phenylethyl	3.50	−2.0
γ-Phenylpropyl	3.60	−1.9

PHENYL KETONES C_6H_5COR R =	$K \times 10^2$	ΔF
		kg.-cal.
Methyl (46%)	130.	+0.2
Ethyl	60	−0.3
n-Propyl (55%)	90	−0.05
n-Butyl	115	+0.1
n-Amyl	130	+0.2
n-Hexyl	145	+0.2
Isopropyl	25	−0.8
Isobutyl	155	+0.3
Isoamyl	155	+0.3
tert-Butyl (91%)	9	−1.4
Cyclohexyl	40	−0.6
Phenyl	No reaction	

CYCLIC KETONES	$K \times 10^2$	ΔF
Cyclopentanone	1.49	−2.4
Cyclohexanone	0.09	−4.1
2-Methylcyclohexanone	0.06	−4.3
3-Methylcyclohexanone	0.30	−3.4
4-Methylcyclohexanone	0.13	−3.9
Cycloheptanone	7.96	−1.5
Menthone	6.54	−1.6
α-Hydrindone	610.0	+1.1
α-Tetralone	806.0	+1.0
Fluorenone	146.	+0.2
Camphor	No appreciable reaction	
Anthrone	No appreciable reaction	
Xanthone	No appreciable reaction	

The conversions obtainable in cyanohydrin formation are largely a function of the structure of the carbonyl compound and are dependent upon the degree of dissociation of the cyanohydrin at equilibrium. The equilibria of a large number of cyanohydrins were first measured by Ultee in the absence of solvents (570) and later with great precision by Lapworth and Manske in 96 per cent ethanol (353). Table 4 presents their data for the dissociation constants (*K*) and thermodynamic stability of cyanohydrins at 20°C. The per cent of cyanohydrin present at equilibrium is given in parentheses for a few compounds.

In benzaldehyde, *o*-nitro, *o*-chloro, or *o*-methoxy substituents stabilize the cyanohydrin. These substituents have little effect in the meta position but have a marked labilizing influence in the para position. Aliphatic ketone cyanohydrins are more highly dissociated than those derived from aldehydes. Cyclization results in a strong stabilizing influence in the case of alicyclic five- and six-membered rings and a labilizing influence in the case of larger rings. Camphor does not form a cyanohydrin. Aryl alkyl ketones are converted to cyanohydrins in poor yields and diaryl ketones not at all. Benzophenone cyanohydrin, which has been prepared by an indirect synthesis, is instantly and completely decomposed by traces of a basic catalyst (608).



$$(C_6H_5)_2\underset{CN}{C}\text{—}\underset{CN}{C}(C_6H_5)_2 \xrightarrow{NO_2} 2(C_6H_5)_2C\begin{smallmatrix}ONO\\ CN\end{smallmatrix} \xrightarrow{H_2O} (C_6H_5)_2C\begin{smallmatrix}OH\\ CN\end{smallmatrix} \xrightarrow{OH^-} (C_6H_5)_2CO + HCN$$

As mentioned earlier, the formation of cyanohydrins from α,β-unsaturated ketones is complicated by the tendency for hydrogen cyanide to add to the olefinic double bond, although no difficulty is encountered with the corresponding aldehydes (399). Cyanohydrin formation of highly enolized ketones such as α-diketones, oxaloacetic esters, and benzoyl acetic esters is usually not successful, although the dicyanohydrin of 1,3-cyclohexanedione is reported (392, 419). While acetoacetic ester readily forms a cyanohydrin, pivaloylacetic ester, $(CH_3)_3COCH_2COOC_2H_5$, does not (582). Similarly, α,α'-dibenzenesulfonylacetone, $C_6H_5SO_2CH_2COCH_2SO_2C_6H_5$, does not add hydrogen cyanide although it gives other ketone reactions (446). α-Dicarbonyl compounds such as camphor quinone and isatin react satisfactorily (80, 256).

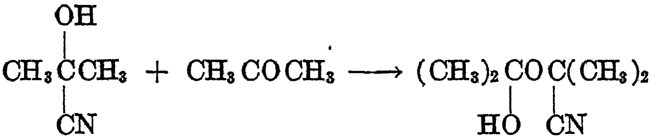
In connection with the discussion of methathesis reactions of alkyl halides and alkali cyanides, it was pointed out that many α-haloketones behave anomalously in forming cyanoölefin epoxides rather than β-ketonitriles (see page 205). Formation of the cyanohydrins of ketones of this type is best effected by the use of Ultee's method (anhydrous hydrogen cyanide). This procedure gives excellent yields with chloroacetone and 2-chloro-3-butanone, while the bisulfite modification fails completely (284, 300).

Aromatic aldehydes in the presence of catalytic amounts of potassium cyanide undergo the benzoin condensation.

$$2C_6H_5CHO \xrightarrow{KCN} C_6H_5COCHOHC_6H_5$$

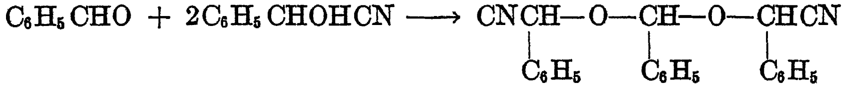
Lapworth (352) and others have felt that this reaction, which cannot be effected by other bases, is closely related to cyanohydrin formation in that the cyanide ion is the active catalyst. This view has been questioned, because the reaction can be effected in non-ionizing solvents (407). More recent kinetic studies have shown that the reaction in these media proceeds concurrently by two mechanisms, i.e., a fast autocatalytic reaction proportional to the amount of benzoin product present and a slow heterogeneous reaction at the surface of the solid catalyst (426). Since the product benzoin may function as an ionizing solvent, Lapworth's mechanism may be partially correct.

The reaction between carbonyl compounds and cyanides may take other courses which lead to contamination of the product. Under the influence of dilute acids, the cyanohydrin will form fairly stable hemiketals with unreacted ketone (569).



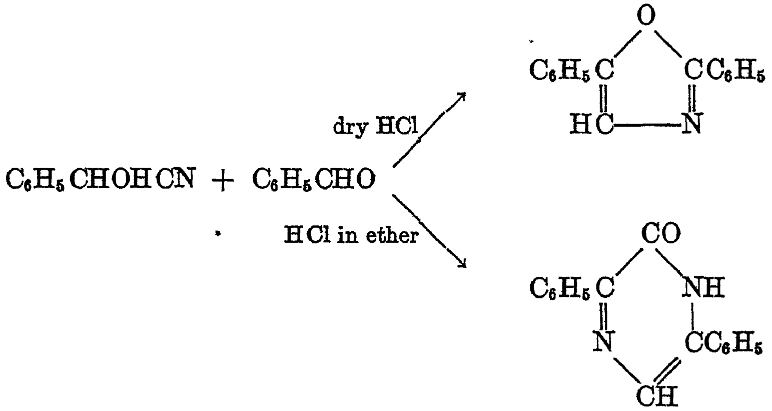
$$CH_3\underset{CN}{\overset{OH}{C}}CH_3 + CH_3COCH_3 \longrightarrow (CH_3)_2\underset{HO}{C}O\underset{CN}{C}(CH_3)_2$$

Considerable quantities of this by-product are often formed in the preparation of ketone cyanohydrins having high dissociation constants (419). With aldehydes a similar side reaction leads to acetal formation (545).



$$C_6H_5CHO + 2C_6H_5CHOHCN \longrightarrow CN\underset{C_6H_5}{CH}-O-\underset{C_6H_5}{CH}-O-\underset{C_6H_5}{CH}CN$$

The latter compound is also formed through deterioration of mandelonitrile (26). The same reagents with dry hydrogen chloride lead to 2,5-diphenyloxazole (184) or 3-keto-2,5-diphenyl-3,4-dihydro-1,4-diazine (287, 292).



The above products may be formed in minor amounts in Ultee's cyanohydrin preparation when anhydrous conditions are employed. In the bisulfite method for the mandelonitrile preparation, still another by-product, *N*-benzylidenemandelamide, $C_6H_5CH{=}NCOCHOHC_6H_5$, is formed from the same reagents (521).

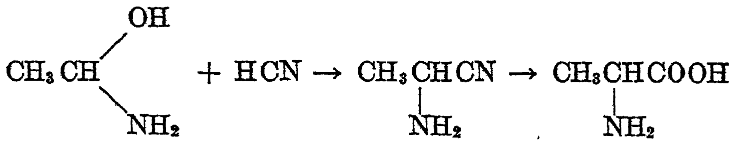
When the reaction is carried out in aqueous solution a certain amount of hydrolysis may be caused by the basicity of the sodium cyanide. The ammonia liberated by this hydrolysis may react with the cyanohydrin to form a variety of products. Thus, Franzen allowed 1200 cc. of formalin to stand with 980 g. of potassium cyanide at room temperature and recovered 130 g. of glycolic acid, 21 g. of glycine, 60 g. of iminodiacetic acid, and 145 g. of iminotriacetic acid. The following reactions account for the formation of these materials, which were obtained in a total yield of 34 per cent (196).

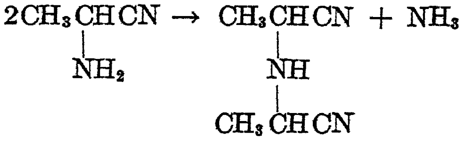
$$\begin{gathered}
KCN + CH_2O + H_2O \rightarrow HOCH_2CN + KOH \\
HOCH_2CN + KOH + H_2O \rightarrow HOCH_2COOK + NH_3 \\
HOCH_2CN + NH_3 \rightarrow NH_2CH_2CN + H_2O \\
NH_2CH_2CN + KOH + H_2O \rightarrow NH_2CH_2COOK \\
NH_2CH_2CN + HOCH_2CN \rightarrow NH(CH_2CN)_2 + H_2O \\
NH(CH_2CN)_2 + 2KOH + 2H_2O \rightarrow NH(CH_2COOK)_2 \\
NH_2CH_2CN + 2HOCH_2CN \rightarrow N(CH_2CN)_3 + 2H_2O \\
N(CH_2CN)_3 + 3KOH + 3H_2O \rightarrow N(CH_2COOK)_3 + 3NH_3
\end{gathered}$$

In the presence of equimolar amounts of calcium chloride the same reagents lead rapidly to the formation of hexamethylenetetramine and glycolic acid, which is precipitated as the calcium salt (323).

$$10CH_2O + 4KCN + 2H_2O \xrightarrow{CaCl_2} (CH_2)_6N_4 + 4HOCH_2COOK$$

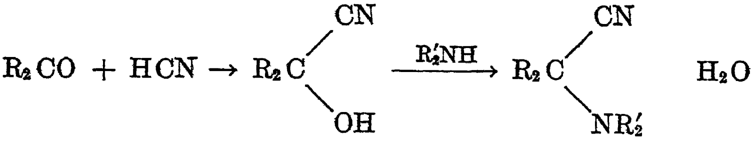
The above reactions lead logically to a consideration of the Strecker synthesis of amino acids, which has proved to be extremely useful to synthetic organic chemists since its discovery in 1850. Strecker treated acetaldehyde ammonia with hydrogen cyanide and hydrolyzed the product to obtain alanine (549). In 1875 Erlenmeyer showed that the intermediate compound in Strecker's synthesis was the α-aminonitrile and that substantial amounts of the iminodinitrile were also formed (176). He further demonstrated that the iminodinitrile is formed by loss of ammonia from two molecules of the aminonitrile (531).





$$2\underset{NH_2}{CH_3CHCN} \rightarrow \underset{\underset{CH_3CHCN}{NH}}{CH_3CHCN} + NH_3$$

In 1880 Tiemann reversed Strecker's order of addition of reagents and caused ammonia to react with the cyanohydrin. He also extended the reaction to ketones and primary and secondary amines (562, 563). Since better yields were obtained in this manner, he preferred to regard the mechanism of the generalized Strecker reaction as proceeding through the cyanohydrin.



This difference of opinion initiated a polemic argument that has been taken up by numerous other investigators over a period of sixty years. Zelinsky and Stadnikoff supported Tiemann's mechanism and introduced the use of a mixture of an alkali cyanide and ammonium chloride as reagents for the preparation of α-aminonitriles (620). The isolation of good yields of the cyanohydrin in the non-aqueous layer of a two-phase Zelinsky–Stadnikoff reaction appears to support this view (4, 111). Sannié, in an elaborate kinetic study of the disappearance of ammonia and hydrocyanic acid from a mixture containing acetaldehyde, found that the irregular reaction rates varied between the rates expected for monomolecular and bimolecular reactions (508). He concluded, on the basis of admittedly ambiguous evidence, that the reaction proceeded by the following sequence:

$$CH_3CHO + H_2O \rightarrow CH_3CH(OH)_2$$
$$CH_3CH(OH)_2 + HCN \rightarrow CH_3CHOHCN$$
$$CH_3CHOHCN + NH_3 \rightarrow CH_3CH(NH_2)CN$$

The study of the principal reaction was confused by the regeneration of ammonia through the formation of the iminodinitrile by-product.

Although it has been demonstrated that aldimines and ketimines will add hydrogen cyanide to give α-aminonitriles (245, 404, 563), it seems improbable that this intermediate is formed in an aqueous mixture of the three reagents under mild conditions.

The original views of Erlenmeyer that the aldehyde ammonia is the intermediate has received the support of Lapworth, who notes that a simple cyanohydrin has acidity comparable to the phenols. The carbon–oxygen bond (strengthened by the cyano substituent) could not be broken in a mild metathesis reaction with ammonia or amines. On the other hand, the aldehyde ammonia has a particularly labile hydroxyl group which should be easily replaced by the cyanide ion (126). Furthermore, since camphor does not form a cyanohydrin (353), the quantitative yield of 1-anilino-1-cyanocamphane obtained from a mixture of camphor, aniline, and potassium cyanide in glacial acetic acid must have been formed through this mechanism (157). These views have received additional support in recent years by the observations of Stewart and coworkers, who have made kinetic studies on the behavior of cyanohydrins in anhydrous media. With amines as catalysts, dissociation of the cyanohydrin to the carbonyl compound and hydrogen cyanide is rapid and reversible. In the opinion of these workers the aldehyde ammonia which then forms is converted to the aminonitrile by reaction with either hydrogen cyanide or a molecule of cyanohydrin (3, 543).

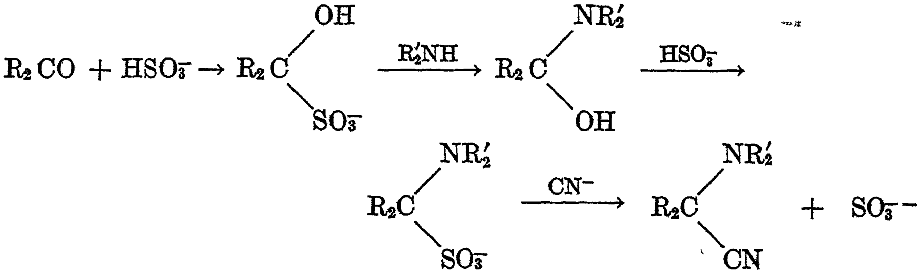
From a practical point of view the Zelinsky–Stadnikoff reagent—ammonium chloride and an alkali cyanide—is popular in modern laboratory practice because of its simplicity. Yields commonly range from 30 to 50 per cent (538). The Tiemann technique of using the cyanohydrin gives very good yields when the formation of iminodinitrile is suppressed by the use of a large excess of anhydrous liquid ammonia (96, 391). With acetone cyanohydrin, yields of aminonitriles vary with the structure of the reacting amine: ammonia (80 per cent), dimethyl-amine (87 per cent), diethylamine (58 per cent), ethylenediamine (40 per cent), cyclohexylamine (70 per cent), and aniline (92 per cent) (289). Methylaniline, however, is reported to be unreactive (420).

The use of ammonium cyanide (232, 526) or of a mixture of hydrogen cyanide and amines (125, 218) is stated to give improved yields. However, α-diketones do not give α-aminonitriles with ammonium cyanide. Benzil is quantitatively cleaved to benzamide and mandelonitrile,

$$C_6H_5COCOC_6H_5 + NH_4CN \rightarrow C_6H_5CONH_2 + C_6H_5CHOHCN$$

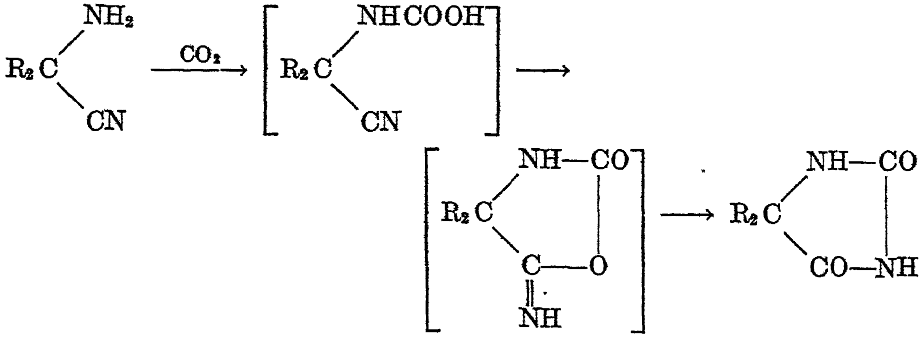
while diacetyl and phenylglyoxal form glyoxaline derivatives (141). The use of glacial acetic acid as a solvent for the reaction of potassium cyanide with the carbonyl compound and the amine gives excellent results (157, 585).

Another modification, which involves the action of an amine and potassium cyanide on the bisulfite addition compound of the aldehyde or ketone, was introduced almost simultaneously by Knoevenagel (313) and Bucherer (94). The method has been used with varying results by a number of investigators (23, 73, 420, 520). In the opinion of Stewart and Li, the mechanism is as follows (543):



Luten has found that the method is best suited to reactions of formaldehyde and lower amines, as indicated in table 5. The yields in parentheses were obtained by the hydrogen cyanide–amine technique (369).

A closely related reaction is the Bucherer synthesis of hydantoins by the interaction of a ketone, hydrogen cyanide, and ammonium carbonate. Since the product is also obtained from the cyanohydrin and ammonium carbonate or from the α-aminonitrile and carbon dioxide, the following mechanism is offered (95):



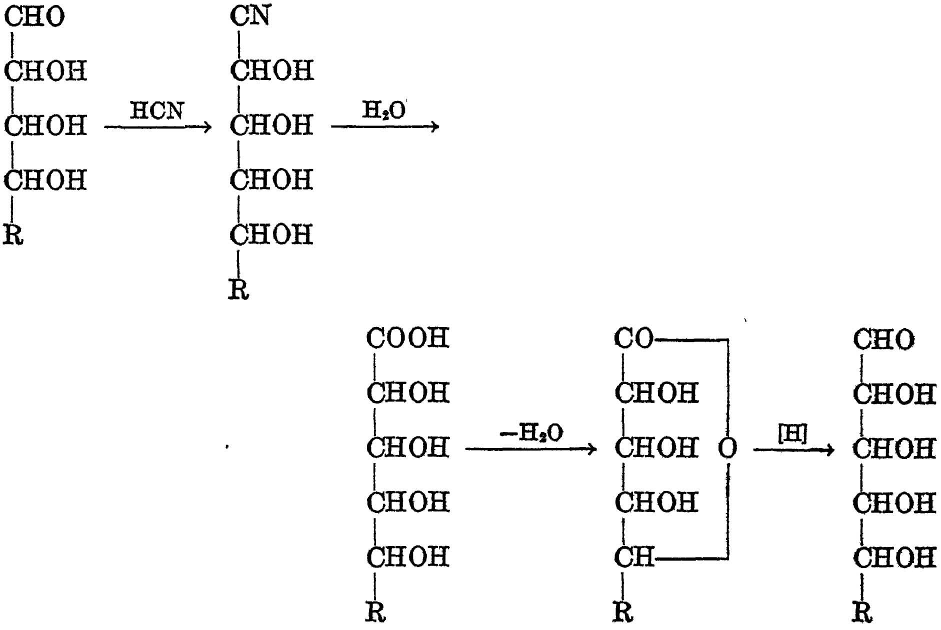
Ketone cyanohydrins give excellent yields, but aryl and alkyl aldehyde cyanohydrins do not.

The addition of hydrogen cyanide to the carbonyl group has proved to be a very useful tool in investigations in the field of carbohydrate chemistry. The well-known Kiliani–Fischer cyanohydrin synthesis (183, 310) of higher carbon sugars has been recently reviewed by Hudson (281).

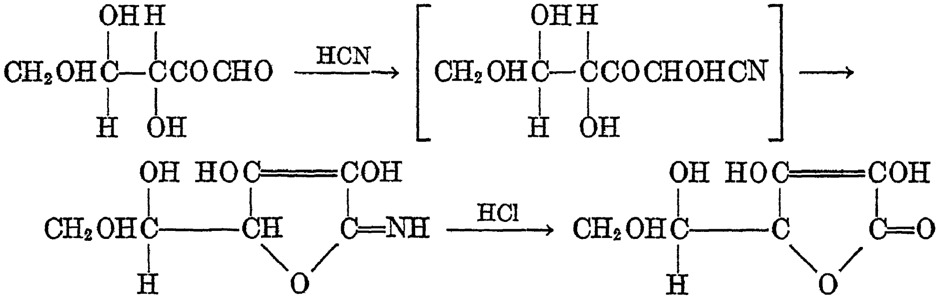
TABLE 5

α-Aminonitriles prepared from bisulfite addition compounds

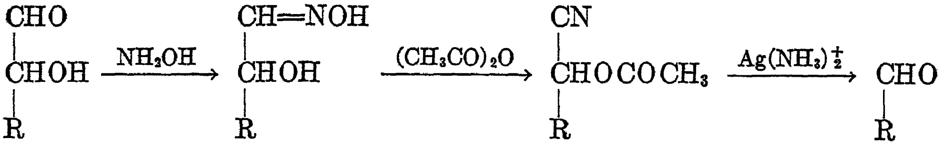
CARBONYL COMPOUND	AMINE	YIELD
		per cent
Formaldehyde	Dimethyl	45–79
Formaldehyde	Diethyl	70–75
Formaldehyde	Di-*n*-propyl	72
Formaldehyde	Diisopropyl	0 (52–65)
Formaldehyde	*n*-Butyl	75
Formaldehyde	Isobutyl	75 (45)
Formaldehyde	*n*-Amyl	84
Formaldehyde	Isoamyl	79
Formaldehyde	*n*-Octyl	0 (31)
Formaldehyde	Methyl phenyl	70–76
Acetaldehyde	Diethyl	25
Acetone	Diethyl	0 (30–39)
Benzaldehyde	Diethyl	56



The Kiliani reaction has been applied by Haworth (253) and Reichstein (479) to the synthesis of *l*-ascorbic acid (vitamin C) from *l*-xylosone. The isolated intermediate in this case is thought to have a cyclic imino structure.



The Wohl degradation of sugars is essentially a reversal of the cyanohydrin synthesis (610).



$$\begin{array}{l}CHO\\|\\CHOH\\|\\R\end{array}\xrightarrow{NH_2OH}\begin{array}{l}CH{=}NOH\\|\\CHOH\\|\\R\end{array}\xrightarrow{(CH_3CO)_2O}\begin{array}{l}CN\\|\\CHOCOCH_3\\|\\R\end{array}\xrightarrow{Ag(NH_3)_2^+}\begin{array}{l}CHO\\|\\R\end{array}$$

When an aqueous solution of an aldehyde or ketone and an alkali cyanide reacts at low temperatures with benzoyl chloride, the cyanomethyl ester is obtained directly (10, 193).

$$CH_2O + NaCN \rightarrow [CNCH_2ONa] \xrightarrow{C_6H_5COCl} C_6H_5COOCH_2CN$$

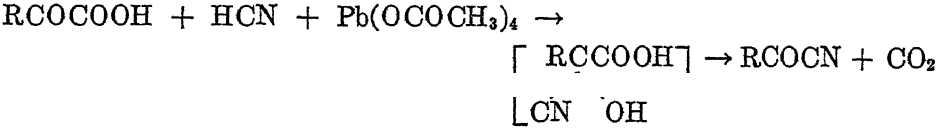
This reaction, which is reminiscent of the Schotten–Baumann esterification technique, gives good yields with α,β-unsaturated aliphatic acid chlorides but not with their saturated analogues (414).

The cyanohydrin synthesis has been used as a convenient route for the conversion of aromatic aldehydes to aryl acetonitriles in good over-all yield (266).

$$C_6H_5CHO \xrightarrow{HCN} C_6H_5CHOHCN \xrightarrow{SOCl_2}$$

$$C_6H_5CHClCN \xrightarrow[CH_3COOH]{Zn} C_6H_5CH_2CN$$

An interesting nitrile synthesis involves the action of hydrogen cyanide and lead tetraacetate upon α-keto acids. The unisolated cyanohydrin is thought to be the intermediate (23a).

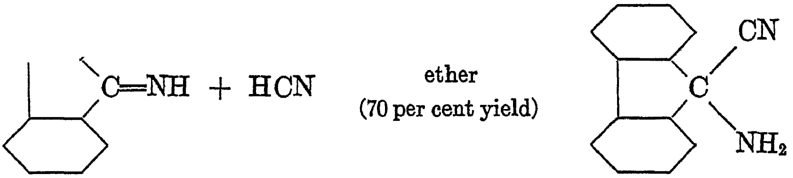


$$RCOCOOH + HCN + Pb(OCOCH_3)_4 \rightarrow \left[\begin{array}{l}RCCOOH\\CN\ \ \ OH\end{array}\right] \rightarrow RCOCN + CO_2$$

The cyanohydrin reaction has also been used as an analytical tool for the estimation of formaldehyde and of carbonyl groups in sugars (367, 403).

C. ADDITION OF HYDROGEN CYANIDE TO CARBON–NITROGEN DOUBLE BONDS

As indicated in the discussion of the Strecker synthesis, hydrogen cyanide will add to the carbon–nitrogen bond of aldimines. This was first demonstrated by Tiemann, although under his aqueous alcoholic conditions it is questionable whether the aldimine or the aldehyde ammonia was the actual reagent (563). Subsequently the reaction was carried out under anhydrous conditions which precluded intermediates of the latter type (245).



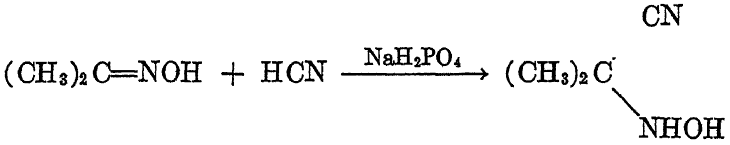
A number of other ketimines behave similarly (404, 530).

Similar additions have been effected with other derivatives of aldehydes and ketones, such as hydrazones (424), semicarbazones, and Schiff bases (221, 404, 492). Methyleneaminoacetonitrile is quantitatively converted to iminodiacetonitrile if catalytic amounts of hydrogen chloride are present (24).

$$(CH_2{=}NCH_2CN)_x + HCN \xrightarrow{(HCl)} NH(CH_2CN)_2$$

The cyanide group is always directed to the carbon atom of a carbon–nitrogen double bond because of the strongly nucleophilic character of the nitrogen atom.

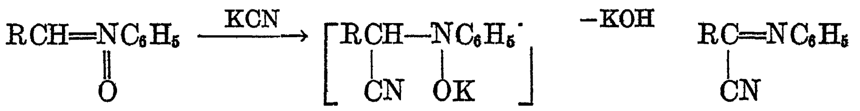
The addition of hydrogen cyanide to aldoximes and ketoximes was effected by Münch in 1896 (424). His yields have been greatly improved by the use of sodium cyanide in an alkali dihydrogen phosphate buffer solution (362, 461).



$$(CH_3)_2C{=}NOH + HCN \xrightarrow{NaH_2PO_4} (CH_3)_2C\begin{matrix} CN \\ NHOH \end{matrix}$$

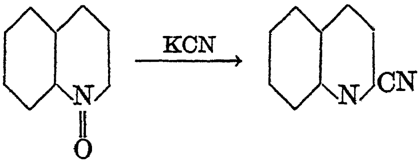
Slightly better results have been obtained by the use of aqueous hydrocyanic acid and a trace of pyridine (2). The use of strongly alkaline potassium cyanide directly usually causes dehydration of the aldoxime to the corresponding nitrile (452).

Bellavita has shown that aldonitrones, the *N*-phenyl ethers of aldoximes, add hydrogen cyanide with the loss of water to form anils of aroyl cyanides. These may be converted by alcoholysis to the anil ester or by hydrolysis to the acyl cyanide (44).



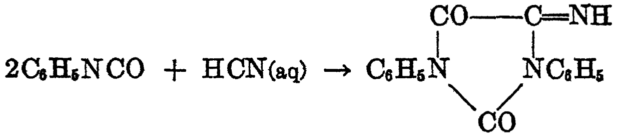
$$\underset{\substack{\| \\ O}}{RCH{=}NC_6H_5} \xrightarrow{KCN} \left[\underset{\substack{| \quad\;\; | \\ CN \;\; OK}}{RCH{-}NC_6H_5}\right] \quad -KOH \quad \underset{\substack{| \\ CN}}{RC{=}NC_6H_5}$$

A similar reaction takes place smoothly with pernitroso derivatives of ketones (452) and with quinoline-*N*-oxide (131, 261).



Phenyl isocyanate adds hydrogen cyanide reversibly in non-aqueous solvents in the presence of alkaline catalysts to form the carbamyl cyanide. The action of aqueous potassium cyanide, however, leads to diphenylparabamide (160).

$$C_6H_5NCO + HCN \rightleftharpoons C_6H_5NHCOCN$$



Aryl isothiocyanates give almost quantitative yields of the thiocarbamyl cyanide even with aqueous potassium cyanide (484).

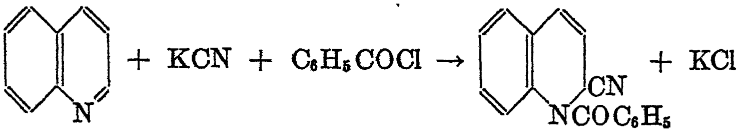
$$C_6H_5NCS + HCN \rightarrow C_6H_5NHCSCN$$

Hydrogen cyanide addition to methyl isothiocyanate must be effected in ether solution with triethylphosphine as a catalyst. Several other basic catalysts are not effective (527).

Diazomethane reacts with hydrogen cyanide to give methyl isocyanide as well as acetonitrile, which was first thought to be the sole product (27, 456).

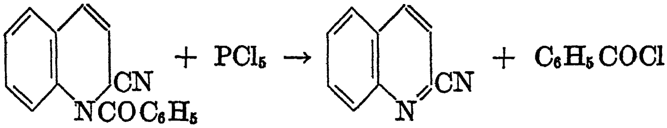
$$CH_2N_2 + HCN \xrightarrow{-N_2} CH_3CN\ (+CH_3NC)$$

Although it is noted earlier that the reaction of benzoyl chloride, hydrogen cyanide, and pyridine constitutes a convenient synthesis of benzoyl cyanide (see page 210), Reissert discovered that quinoline, benzoyl chloride, and aqueous potassium cyanide led to the formation of 1-benzoyl-2-cyanodihydroquinoline (483).

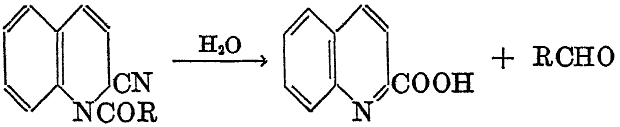


Other cyclic bases such as pyridine, benzothiazole, and acridine did not give satisfactory results, but isoquinoline forms 1-cyano-2-benzoyldihydroisoquinoline. Reissert's reaction has been variously represented as proceeding through such improbable intermediates as 1-benzoyl-2-chlorodihydroquinoline or benzoyl cyanide. Recent studies in non-aqueous solvents, however, indicate that the mechanism probably involves the addition of hydrogen cyanide to the carbon–nitrogen double bond, followed by acylation of the resultant secondary amine.

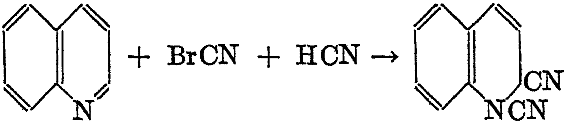
It has been observed that the reaction with potassium cyanide proceeded satisfactorily for aroyl or cinnamoyl chloride in liquid sulfur dioxide solution, but not in benzonitrile, ether, dioxane, acetone, or chloroform (616). Grosheinz and Fischer have extended the reaction to include aliphatic acid chlorides by the use of hydrogen cyanide and 2 moles of quinoline in absolute benzene solution. Yields range from 10 to 74 per cent for these compounds and from 80 to 96 per cent for aroyl chlorides (230). Treatment of Reissert's compound with phosphorus pentachloride in a diluent such as chloroform regenerates the benzoyl chloride with the formation of 2-cyanoquinoline in 55–70 per cent yields (306).



The compound may be hydrolyzed by sulfuric or hydrochloric acid to the aldehyde and quinaldic acid. This convenient aldehyde synthesis has been applied to a large number of acid chlorides in high over-all yield (230, 306, 552).

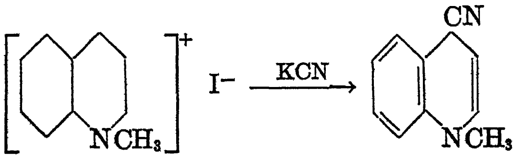


A closely related reaction is that of Mumm and coworkers, who obtained a mixture of *cis*- and *trans*-1,2-dicyanodihydroquinolines from hydrogen cyanide, cyanogen bromide, and excess quinoline in benzene solution.

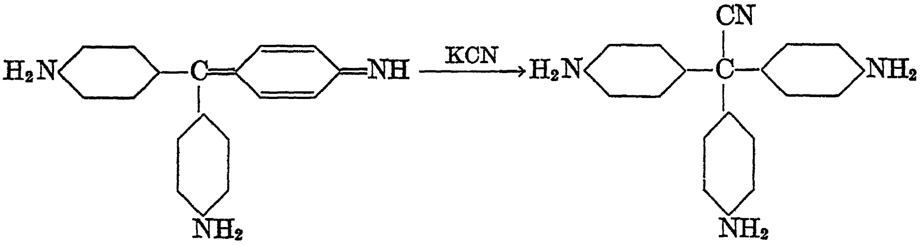


Isoquinoline gives a dicyanide, while 2-substituted quinolines react at higher temperatures to give 4-cyanoquinoline derivatives (422, 423). There are indications that a 1,4-addition of hydrogen cyanide to pyridine takes place, since traces of 4-cyanopyridine have been detected in reactions of organic halides with cuprous cyanide in pyridine solution (419).

Hydrogen cyanide has been reported to add in a 1,4 manner to quinoline methiodide (307).



Pararosaniline and hydrogen cyanide lead to the formation of the highly dissociated tris(*p*-aminophenyl)acetonitrile (360).

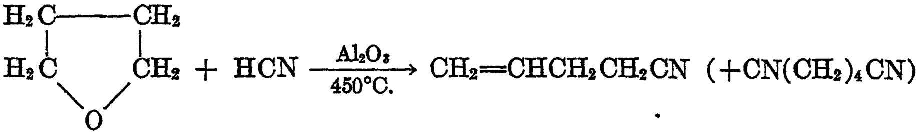


D. HYDROCYANOLYSIS OF CARBON–OXYGEN BONDS

The hydrocyanolysis of simple *aliphatic ethers* apparently occurs only in the vapor phase at elevated temperatures.

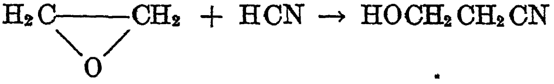
$$C_2H_5OC_2H_5 + 2HCN \rightarrow 2C_2H_5CN + H_2O$$

The preferred conditions are temperatures of 300–500°C. and dehydration catalysts such as alumina, silica, thoria, or the phosphate and borate salts of numerous metals (11, 286, 433). Tetrahydrofuran undergoes a similar reaction, forming allylacetonitrile (30 per cent), adiponitrile (8 per cent), pyridine (10 per cent), and α-aminopyridine (2 per cent)(561).



Ethylene oxide is reported to react under similar conditions to give succinonitrile (613).

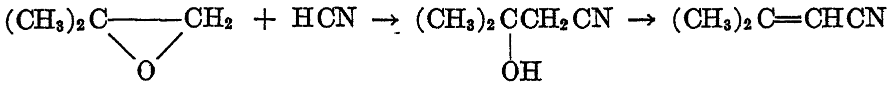
Olefin oxides of the latter type, however, react rapidly and exothermally (40–50 kg.-cal. per mole) with hydrogen cyanide at low temperature to give the corresponding cyanohydrins in nearly quantitative yield.



This reaction was first observed in 1878 by Erlenmeyer, who allowed the reagents to stand for several weeks at room temperature (175). The catalytic effect of bases was not observed until much later (181, 475). In the absence of alkaline catalysts a vigorous reaction is not initiated below about 150°C. (149).

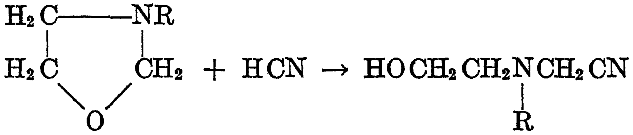
Methods of generating hydrogen cyanide in an aqueous alkali cyanide reaction mixture involve the use of carbon dioxide gas (84) or a saturated solution of magnesium sulfate (556). Modern industrial practice, however, favors the use of anhydrous reagents in the presence of a trace of basic catalysts such as sodium cyanide. This technique was employed for the production of ethylene cyanohydrin in nearly quantitative yield on a very large commercial scale before the recent adoption of the direct synthesis of acrylonitrile from acetylene and hydrogen cyanide (see page 224).

With substituted olefin oxides, the direction of addition favors the production of secondary or tertiary cyanoalcohols (84, 475). This is demonstrated by the fact that 2-methylpropene epoxide gives a hydroxynitrile which is easily dehydrated on distillation to the unsaturated nitrile (84). The alternate addition product would have been a stable cyanohydrin.

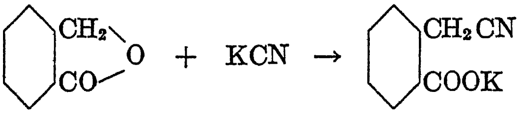


The reaction of 2-chloro-1-propanol with potassium cyanide was thought to proceed through propylene oxide as an intermediate, since β-hydroxy-*n*-butyronitrile was the product (158). Attempts to reverse the direction of addition by the use of acidic catalysts (as has been done in the addition of alcohols to olefin oxides) have not been successful (419). 2-Methyl-2,3-epoxybutyronitrile is stated to be inert toward hydrogen cyanide (215).

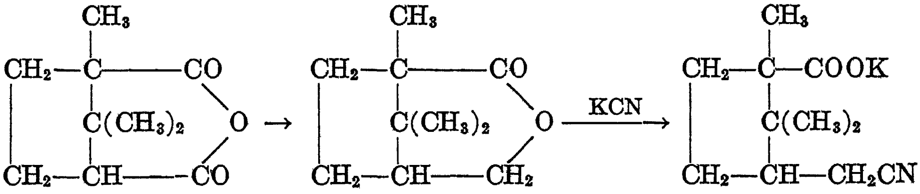
Certain heterocyclic compounds, such as oxazolidines, add hydrogen cyanide very easily at low temperatures (568).



The reaction of *lactones* with alkali cyanides was observed in 1886 by Wislicenus, who obtained 90–95 per cent yields of the mononitrile of homophthalic acid from the reaction of phthalide and potassium cyanide at 180–190°C. (466, 603).

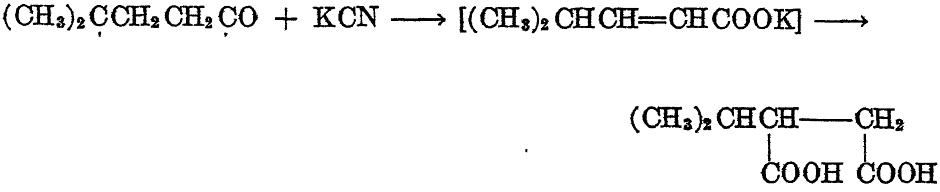


Camphoric anhydride has similarly been converted to campholide and homocamphoric mononitrile, a series of reactions which played a part in the final proof of Brett's structure for camphor (237, 500).



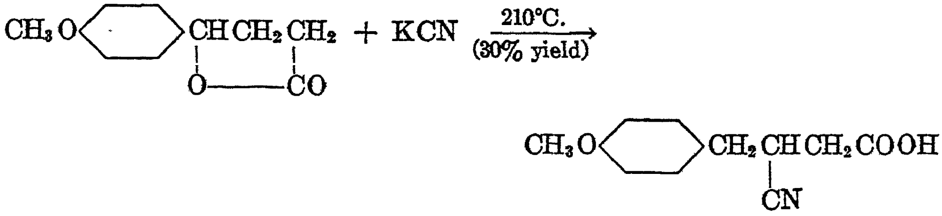
A number of other phthalide derivatives and aliphatic lactones react similarly (1, 51, 52, 328, 332).

Blaise observed that isocapro-γ-lactone gave rise to isopropylsuccinic acid instead of the expected α,α-dimethylglutaric acid (51). This material undoubtedly arose through formation of the α,β-unsaturated acid (by dehydration and isomerization), which added hydrogen cyanide in the normal α,β fashion.

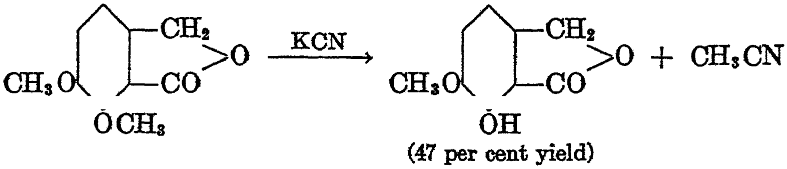


$$(CH_3)_2CCH_2CH_2CO + KCN \longrightarrow [(CH_3)_2CHCH{=}CHCOOK] \longrightarrow (CH_3)_2CH\underset{COOH}{CH}{-}\underset{COOH}{CH_2}$$

γ-*p*-Anisyl-γ-butyrolactone undergoes a similar rearrangement before addition (464).



The rather drastic alkaline conditions of this reaction sometimes cause other side-reactions. Meconin does not react at the lactone group but does lose one of its methoxy groups (490).



Aliphatic esters do not appear to have been investigated. In this connection, propionitrile has been isolated in a study of the action of potassium cyanide on isobutyraldehyde in alcohol solution. Presumably it was formed by the action of potassium cyanide on ethyl isobutyrate, which arose through disproportionation and esterification of the aldehyde (555).

V. ISOCYANIDE ISOMERIZATION AND RELATED SYNTHESES

The isomerization of isocyanides to nitriles by the action of heat was first observed by Gautier in 1867 (210) in connection with his studies on the reaction of alkyl halides with metal cyanides (see page 195). Further studies by Nef indicated that ethyl isocyanide is completely converted to propionitrile in 3 hr. at 230–255°C., while phenyl isocyanide forms benzonitrile in 2 hr. at 200–220°C. (429). In 1907 Guillemard investigated the molecular weights and products of the reaction at various temperatures and found that isomerization and reversible polymerization of isocyanides proceed simultaneously. With ethyl isocyanide the polymerization reaction begins at 120°C., reaches a maximum at 160°C., and is reversed at 220°C. Isomerization to nitriles begins at 140°C. and is complete at 240°C. These findings led to the hypothesis that the isomerization reaction proceeds through the trimer (231).

$$\mathrm{RNC} \rightarrow (\mathrm{RNC})_3 \rightarrow \mathrm{RCN}$$

The heats of combustion of isocyanides range from 15 to 20 cal. per mole higher than for the corresponding nitriles (356). The thermodynamic aspects of the structures of these two classes of compounds have been discussed by Pauling and Hendricks (454).

A number of syntheses of nitriles have been effected which utilize amines and their derivatives. Some of these reactions involve a carbon–nitrogen rearrangement of the type discussed above. Moderate yields of aromatic nitriles are obtained, but the methods are of very little value in the aliphatic series.

Pyrolysis of *N*-ethylaniline at 560°C. results in the production of a 35 per cent yield of benzonitrile, together with hydrogen and unsaturated hydrocarbons. This derivative is a more satisfactory reagent than the *N*-methyl- (8 per cent yield of benzonitrile), *N*-propyl- (24 per cent yield), *N*-butyl- (4 per cent yield), or *N*,*N*-dimethyl-anilines (4 per cent yield)(595).

$$\mathrm{C_6H_5NHC_2H_5} \rightarrow \mathrm{C_6H_5CN} + \mathrm{H_2} + \mathrm{CH_4}$$

Hofmann noted in 1867 that formanilide when heated with zinc dust gave rise to benzonitrile (270). This method has attracted the interest of subsequent workers, and it is stated in the patent literature that aniline is transformed by formic acid over activated carbon or silica gel at 450°C. to benzonitrile in conversions of 25 per cent. By similar techniques phenylacetonitrile is obtained from benzylamine (42 per cent conversion), *m*-tolunitrile from *m*-toluidine (40 per cent conversion and 88 per cent yield), and *o*-tolunitrile from *o*-toluidine (55 per cent conversion and 82 per cent yield)(434).

$$\mathrm{C_6H_5NH_2} + \mathrm{HCOOH} \xrightarrow{-\mathrm{H_2O}} \mathrm{C_6H_5NHCHO} \xrightarrow{-\mathrm{H_2O}} \mathrm{C_6H_5CN}$$

Distillation of aniline oxalate also gives low yields of benzonitrile (271, 564).

The distillation of aryl isothiocyanates or diarylthioureas over metals such as copper, zinc, or iron produces aryl cyanides, with the simultaneous formation of metallic sulfides (432, 522, 590).

$$\mathrm{C_6H_5SCN} + \mathrm{Cu} \rightarrow \mathrm{C_6H_5CN} + \mathrm{CuS}$$

A similar result is obtained by heating bromobenzene with copper thiocyanate at 180°C. for 8–9 hr. in pyridine solution. Benzonitrile is obtained in 23 per cent yield in the presence of pyridine, together with 39 per cent of a mixture of diphenyl sulfide and diphenyl disulfide (493).

VI. AMINE DEHYDROGENATION

Interest in the dehydrogenation of amines as a method of preparing nitriles was initiated in 1884 when Hofmann published the results of his studies of the action of bromine and aqueous alkali on the amides of carboxylic acids. With aliphatic amides of five carbon atoms or less, the principal product of the reaction is the amine of one less carbon atom. With amides of more than five carbon atoms the resultant amine is further attacked by the reagent and, by a bromination–dehydrobromination mechanism, is converted to the nitrile.

The reaction has limitations as a preparative method because the yields are not high, reaching a maximum of 25–30 per cent with the amides of pelargonic and capric acids. Substituted ureas are by-products in the Hofmann degradation (273).

$$RCH_2CONH_2 + Br_2 + KOH \rightarrow RCH_2CONHBr + KBr + H_2O$$

$$RCH_2CONHBr + KOH \rightarrow [RCH_2CON] + KBr + H_2O$$

$$[RCH_2CON] \rightarrow RCH_2NCO$$

$$RCH_2NCO + 2KOH \rightarrow RCH_2NH_2 + K_2CO_3$$

$$RCH_2NH_2 + 2Br_2 + 2KOH \rightarrow RCH_2NBr_2 + 2KBr + 2H_2O$$

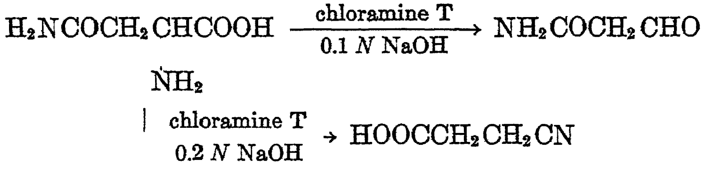
$$RCH_2NBr_2 + 2KOH \rightarrow RCN + 2KBr + 2H_2O$$

Phenylpropiolamide is a special case in which good yields of phenylacetonitrile are obtained.

$$C_6H_5C{\equiv}CCONH_2 \xrightarrow{NaOBr} [C_6H_5C{\equiv}CNH_2] \longrightarrow C_6H_5CH_2CN$$

The dehydrochlorination of alkyldichloroamines, which parallels the last phase of the Hofmann degradation, has been effected by alkalies (29, 39) and by magnesium (101).

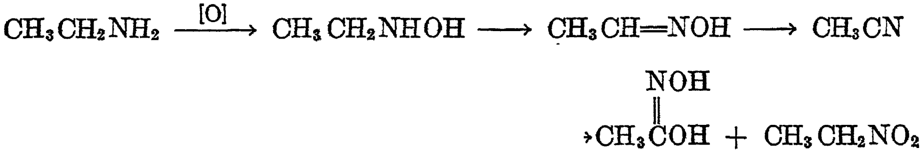
Closely related to the above is Dakin's reaction of chloramine T (sodio-*p*-toluenesulfochloroamide) with α-amino acids. In weakly alkaline solution at 20°C. the degradation leads to the aldehyde, but in slightly stronger alkali (0.2 *N*) at 35°C. the nitrile is the principal product. Histidine, glycine, alanine, and α-aminophenylacetic acid are all converted to the nitriles in varying yields by this reaction, which is illustrated below for glutamic acid (83, 139, 140).



$$H_2NCOCH_2\underset{\displaystyle NH_2}{CH}COOH \xrightarrow[0.1\,N\ NaOH]{\text{chloramine T}} NH_2COCH_2CHO$$

$$\xrightarrow[0.2\,N\ NaOH]{\text{chloramine T}} HOOCCH_2CH_2CN$$

Bamberger has observed that monopersulfuric acid oxidizes aliphatic amines to nitriles in rather low yields. Oximino acids and nitro compounds are by-products and the latter are formed exclusively in the aromatic series (28).



$$CH_3CH_2NH_2 \xrightarrow{[O]} CH_3CH_2NHOH \longrightarrow CH_3CH{=}NOH \longrightarrow CH_3CN$$

$$\rightarrow CH_3\overset{\displaystyle NOH}{\overset{\|}{C}}OH + CH_3CH_2NO_2$$

The vapor-phase dehydrogenation of amines was studied first by Sabatier (502) and Maihle (379) in 1917. The amine is passed over hydrogenation catalysts such as finely divided nickel at 300–350°C. or copper at 450°C. Benzylamine forms about 30 per cent benzonitrile, together with by-product toluene which arises through hydrogenolysis of the amine.

$$C_6H_5CH_2NH_2 \;-\!\!\left\{\begin{array}{l} \xrightarrow{-H_2} C_6H_5CN \\[1em] \xrightarrow{+H_2} C_6H_5CH_3 + NH_3 \end{array}\right.$$

Except for the lowest members of the series, the aliphatic amines give much better yields of nitriles, a nearly quantitative yield being obtained from isoamylamine. In general, copper was found to be a less satisfactory catalyst than nickel. Secondary and tertiary amines are pyrolyzed to olefins and nitriles.

$$((CH_3)_2CHCH_2CH_2)_2NH \rightarrow (CH_3)_2CHCH_2CN + (CH_3)_2CHCH{=}CH_2 + H_2$$

Schiff bases behave similarly, a mixture of toluene, ethylene, benzonitrile, and acetonitrile being obtained from *N*-ethylbenzaldimine.

By passing the amine and ammonia simultaneously over the catalyst, the nitrile–hydrocarbon ratio in the product is increased (36). Other catalysts for this reaction are the sulfides or arsenides of zinc and cadmium, which are effective at 500°C. (370). Although the intermediate aldimine has never been isolated, its presence was detected when the reaction vapors were diluted with steam, which caused hydrolysis to the aldehyde (401).

The formation of by-product hydrocarbons through hydrogenolysis of the amine has also been effectively reduced by simultaneously introducing a controlled amount of oxygen or air into the system. By this oxidation technique, methallylamine has been converted to methacrylonitrile in 72–76 per cent conversions and 85–88 per cent yields at 500–575°C. over a silver catalyst. Acrylonitrile is similarly obtained from allylamine (385). Nicotine is oxidized over vanadium pentoxide to nicotinonitrile in 52 per cent yield (615).

Another technique for removing the by-product hydrogen is by the use of an acceptor such as an easily hydrogenated olefin. From butylamine, ammonia, and 2-pentene at 180–200°C. in an autoclave in the presence of a cobalt catalyst is obtained a 70 per cent yield of butyronitrile (442).

Several similar high-temperature dehydrogenation techniques are reported in which the amine or aldimine is undoubtedly formed but not isolated. Thus, amides when passed over nickel catalysts at high temperatures are degraded to the amines through loss of carbon monoxide. If the amine formed is primary and aliphatic, it is simultaneously dehydrogenated to the nitrile. The reaction is essentially a vapor-phase catalytic degradation of the Hofmann type (377).

$$RCH_2CONH_2 \xrightarrow{Ni} CO + [RCH_2NH_2] \longrightarrow RCN + H_2$$

Isobutyraldehyde, isovaleraldehyde, propionaldehyde, benzaldehyde, and anisaldehyde have been converted in 30–40 per cent yields by ammonia over thoria at 220–240°C. to the nitriles through the aldimine intermediates (379).

$$RCHO + NH_3 \xrightarrow{-H_2O} [RCH{=}NH] \xrightarrow{-H_2} RCN$$

Similarly, alcohols and ammonia are converted to nitriles by the method of Hara and Komatsu over finely divided copper or silver catalysts at 300–400°C. Amines and aldimines are assumed to be intermediates in this synthesis, which gives 55–90 per cent yields (243, 536).

$$\mathrm{RCH_2OH + NH_3 \xrightarrow[300\text{–}400°\mathrm{C.}]{\mathrm{Cu}} [RCH_2NH_2] \longrightarrow [RCH{=}NH] \longrightarrow RCN + H_2O + 2H_2}$$

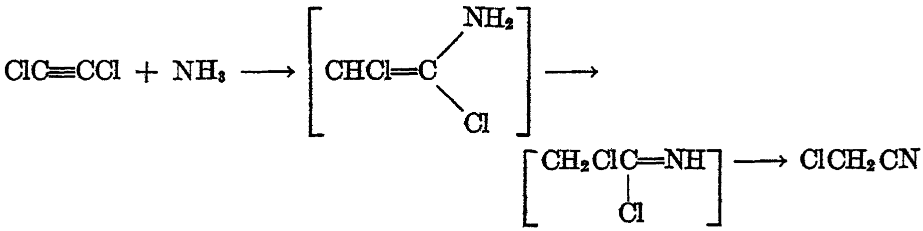
Maihle has found that alkyl nitrites and nitroalkanes may be converted by hydrogen at 300°C. over nickel catalysts to the corresponding nitriles by an ingenious hydrogenation–dehydrogenation technique (379).

$$\mathrm{RCH_2NO_2 \xrightarrow{3H_2} [RCH_2NH_2] \xrightarrow{-2H_2} RCN}$$

The preparation of acetonitrile from acetylene and ammonia was studied by Chichibabin (110) and has been voluminously discussed in the patent literature (435, 513, 550, 551).

$$\mathrm{CH{\equiv}CH + NH_3 \rightarrow [CH_2{=}CHNH_2] \rightarrow [CH_3CH{=}NH] \rightarrow CH_3CN}$$

Considerable amounts of pyridine, picolines, pyrrole, and related compounds are also formed. A recent publication indicates that a 66 per cent yield of acetonitrile is obtained over a zirconium oxide catalyst at 400–500°C. A trace of water vapor is essential for high yields (10a). A special case is found in the action of ammonia on an ether solution of dichloroacetylene. Chloroacetonitrile results by dehydrohalogenation of the unisolated intermediate iminochloride (445).



$$\mathrm{ClC{\equiv}CCl + NH_3 \longrightarrow \left[CHCl{=}C{\Large\langle}\begin{matrix}NH_2\\ Cl\end{matrix}\right] \longrightarrow \left[CH_2ClC(Cl){=}NH\right] \longrightarrow ClCH_2CN}$$

A recent development involves the amination of olefins with the simultaneous formation of amines and the nitriles resulting from their dehydrogenation. Temperatures of 200–350°C., pressures up to 500 p.s.i., and a supported cobalt catalyst promoted by manganese dioxide are stated to give the best results (558).

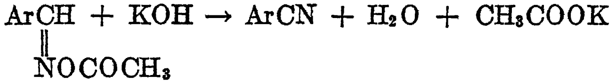
The commercial production of benzonitrile from toluene and ammonia by a high-temperature catalytic vapor-phase process has recently been announced (12b). Undoubtedly benzylamine and benzaldimine are intermediates.

$$\mathrm{C_6H_5CH_3 + NH_3 \rightarrow [C_6H_5CH_2NH_2] \rightarrow [C_6H_5CH{=}NH] \rightarrow C_6H_5CN + 3H_2}$$

VII. Dehydration of Oximes

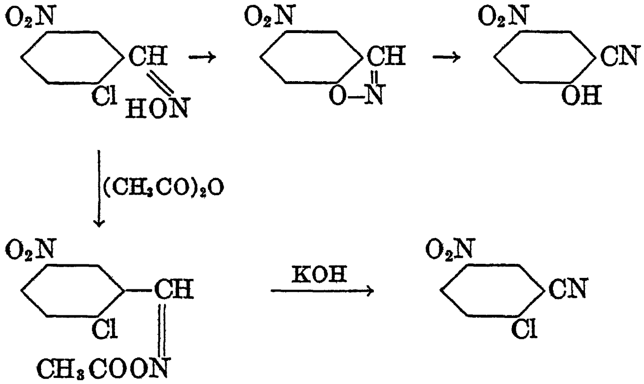
The dehydration of aldoximes is a facile method of synthesis which permits the transformation of an aldehyde to the corresponding nitrile under mild reaction conditions in high over-all yield. The reaction was first observed by Gabriel and Meyer in 1881, who used refluxing acetic anhydride (203). This is still the most popular reagent for effecting the dehydration, but thionyl chloride (409), ethyl chloroformate (67), lead oxide (56), phosphorus pentoxide (517), benzenesulfonyl chloride (192), alkalies (115), and heat alone (115, 379) are representative of the many types of reagents that have been used.

In 1891 Hantzsch studied the two isomeric forms of aldoximes and noted that the acetyl derivative of one form (α) regenerated the aldehyde on treatment with alkali, whereas the other form (β) was converted to the nitrile. On the assumption that nitrile formation was the result of a "*cis*" elimination of acetic acid, he arbitrarily assigned the *syn*-structure to the β-oxime.



$$\underset{\displaystyle \text{NOCOCH}_3}{\overset{}{\text{ArCH}}}\!\!\Vert + \text{KOH} \rightarrow \text{ArCN} + \text{H}_2\text{O} + \text{CH}_3\text{COOK}$$

Subsequently, evidence of various types has been accumulated to show that the structures of Hantzsch were erroneous. For example, Brady and Bishop showed that the isomer of 2-chloro-5-nitrobenzaldoxime, whose acetate lost acetic acid readily, also was the one which underwent ring closure to form the isoxazole and ultimately the hydroxynitrile (66). Since neighboring groups undoubtedly react most readily in ring closures, the acetic acid elimination must proceed by a "*trans*" elimination mechanism.



Acetic anhydride does not cause inversion during acetate formation (67). This structural problem has attracted the attention of numerous investigators, most of whom now appear to be in agreement that the α-oxime has the *syn*-configuration (250).

Hauser and coworkers have studied in considerable detail the effect of alkaline agents on *syn*- and *anti*-oximes and their derivatives. The products obtained from each isomer depend largely upon the conditions employed. Thus *anti*-benzaldoxime acetate forms the nitrile predominantly at 30°C., but at 0°C. principally regenerates the oxime.

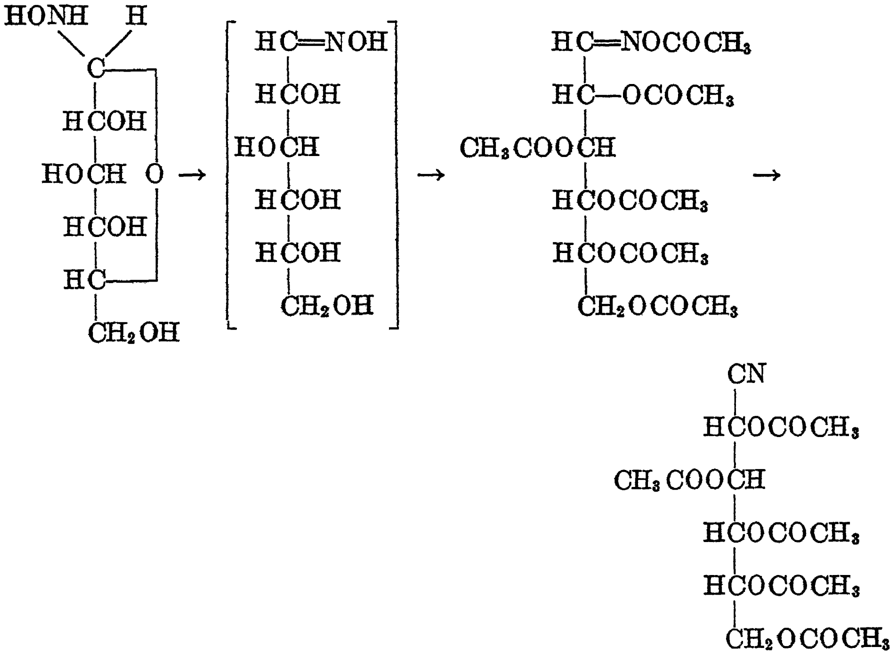
Furthermore, even the *syn*-compounds will react at 100°C. to give nitriles (250). In general, the oxime carbonates give higher yields of nitriles than the acetates (251). Studies of the action of benzoyl chloride on *syn*- and *anti*-oximes have led to the conclusion that an equilibrium exists under basic conditions between the *syn*- and *anti*-benzoates. The *anti*-benzoate is thought to be the immediate precursor of the nitrile, although it could not be isolated under the reaction conditions employed (252).

$$\begin{tikzcd} \textit{anti}\text{-oxime} \arrow[r, "C_6H_5COCl", "\text{pyridine}"'] & {[\textit{anti}\text{-oxime benzoate}]} \arrow[r] \arrow[d, shift right] & \text{nitrile} \\ \textit{syn}\text{-oxime} \arrow[r, "C_6H_5COCl", "\text{pyridine}"'] & \textit{syn}\text{-oxime benzoate} \arrow[u, shift right] & \end{tikzcd}$$

Hauser has also studied chloramine as a reagent for converting aromatic aldehydes to nitriles. The intermediate aldchlorimine is converted almost instantaneously at 0°C. by bases to the nitrile in high yield (249).

$$ArCHO + NH_2Cl \rightarrow ArCH{=}NCl \xrightarrow{\text{base}} ArCN$$

The oxime dehydration method is particularly useful for nitrile synthesis in cases where the molecule contains sensitive groups that would be attacked under more drastic reaction conditions. In many cases it is the only method of preparation available. The reaction is the first step in the Wohl degradation of sugars, and glucose may be converted in 50–55 per cent over-all yield to pentaacetyl-*d*-gluconitrile (117, 610). By suitable modifications gluconitrile itself may be obtained in similar yield (611, 621). Wolfrom has shown that glucose oxime, which normally exists in a ring-type structure, is cleaved to form the open-chain hexaacetate before the nitrile is formed by loss of acetic acid (612a).



Nitroacetonitrile had been the structure erroneously proposed by Kekulé for fulminic acid, and its independent synthesis was attempted unsuccessfully by a large number of investigators. This was ultimately accomplished by the thionyl chloride dehydration of nitroacetaldehyde oxime and was shown to be an unstable oil which had no relation to fulminic acid (539).

$$NO_2CH_2CH{=}NOH \xrightarrow{SOCl_2} NO_2CH_2CN$$

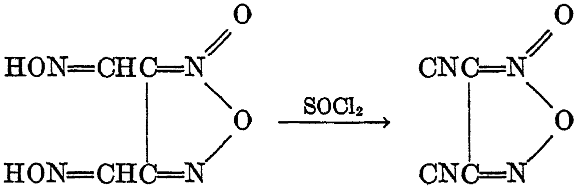
The oxime dehydration method is advantageous for the preparation of acyl cyanides. This is especially true for aroyl cyanides, since the requisite intermediates for these preparations are easily obtained from aryl methyl ketones (60, 63, 115, 517).

$$ArCOCH_3 \xrightarrow{C_5H_{11}ONO} ArCOCH{=}NOH \rightarrow ArCOCN$$

Carbonyl cyanide is obtained from dioximinoacetone (381).

$$HON{=}CHCOCH{=}NOH \xrightarrow{(CH_3CO)_2O} CH_3COON{=}CHCOOCH{=}NOCOCH_3 \rightarrow CNCOCN$$

Cyano derivatives of various heterocyclic compounds such as pyrroles (186), quinolines (59), furans (599), and thiophenes (166) are prepared by this method. Dicyanofuroxan is obtained from the appropriate dioxime in 30–40 per cent yields (504).

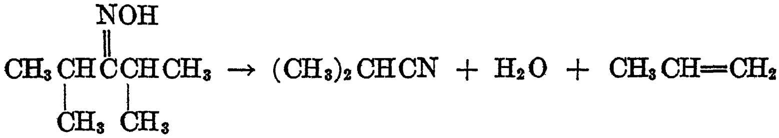


Oximes of unsaturated aldehydes are dehydrated without causing polymerization or isomerization in the configuration or position of the double bond (417, 624). Propionaldoxime undergoes simultaneous catalytic dehydration and dehydrogenation to acrylonitrile (172).

$$CH_3CH_2CH{=}NOH \xrightarrow[400°C.]{Cr_2O_3} CH_2{=}CHCN + H_2O + H_2$$

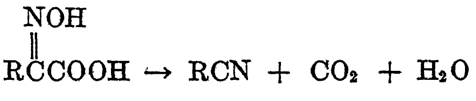
It is possible to distinguish between aldehydes and ketones and separate them on the basis of the stability of their oximes. This procedure has proved to be useful in structural studies of certain natural products (337).

When subjected to drastic pyrolytic conditions, however, even ketoximes can be converted to nitriles (379).



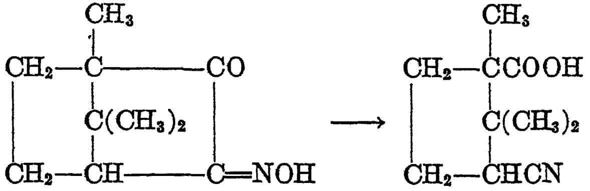
$$CH_3\underset{\displaystyle CH_3}{CH}\overset{\displaystyle NOH}{\overset{\|}{C}}\underset{\displaystyle CH_3}{CH}CH_3 \rightarrow (CH_3)_2CHCN + H_2O + CH_3CH{=}CH_2$$

The yields are poor unless the oximino group is adjacent to another carbonyl, carboxyl, or carbinol group. In these cases cleavage of the carbon–carbon bond proceeds at lower temperatures and in much better yield. Thus, α-oximino acids are readily degraded by dilute acids to a nitrile having one less carbon atom (586a):

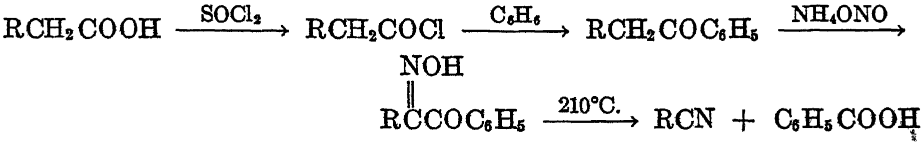


$$R\overset{\displaystyle NOH}{\overset{\|}{C}}COOH \rightarrow RCN + CO_2 + H_2O$$

Isonitrosocamphor is converted in 85 per cent yield to camphoric acid mononitrile (324, 504).

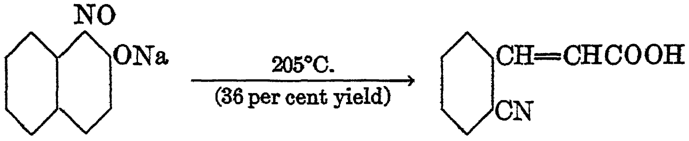


The following sequence of reactions has been used for the synthesis of aliphatic nitriles of more than five carbon atoms (145):



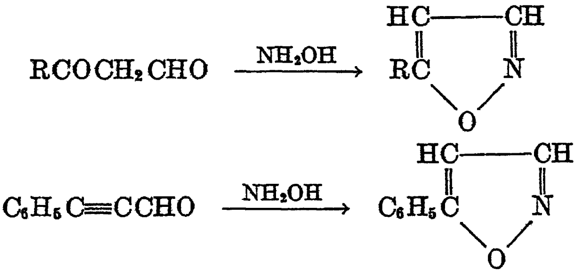
$$\mathrm{RCH_2COOH} \xrightarrow{\mathrm{SOCl_2}} \mathrm{RCH_2COCl} \xrightarrow{\mathrm{C_6H_6}} \mathrm{RCH_2COC_6H_5} \xrightarrow{\mathrm{NH_4ONO}} \mathrm{R\overset{\overset{\displaystyle NOH}{\|}}{C}COC_6H_5} \xrightarrow{210°\mathrm{C.}} \mathrm{RCN} + \mathrm{C_6H_5COOH}$$

The preparation of *o*-cyanocinnamic acid by heating the sodium salt of α-nitroso-β-naphthol is a related reaction (148).

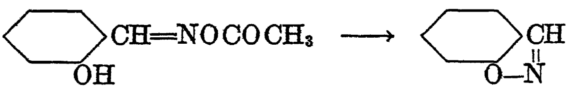


The older literature on the pyrolysis of ketoximes has been discussed at length by Hurd (282).

β-Ketoaldehydes and derivatives of propiolaldehyde form isoxazoles when treated with hydroxylamine (22, 114).

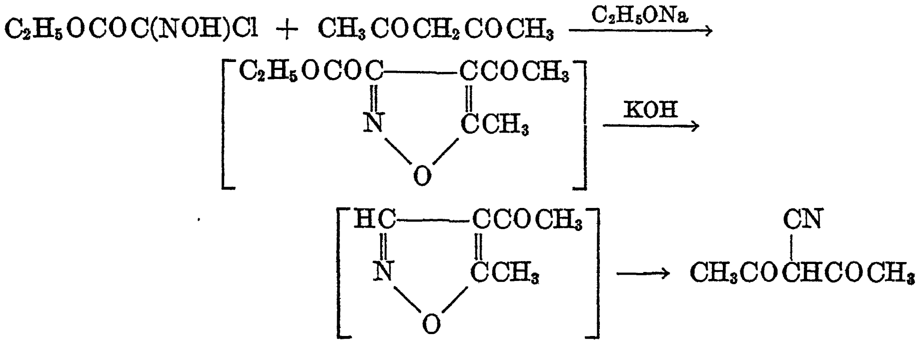


A similar reaction takes place with *o*-hydroxybenzaldoxime derivatives (363).

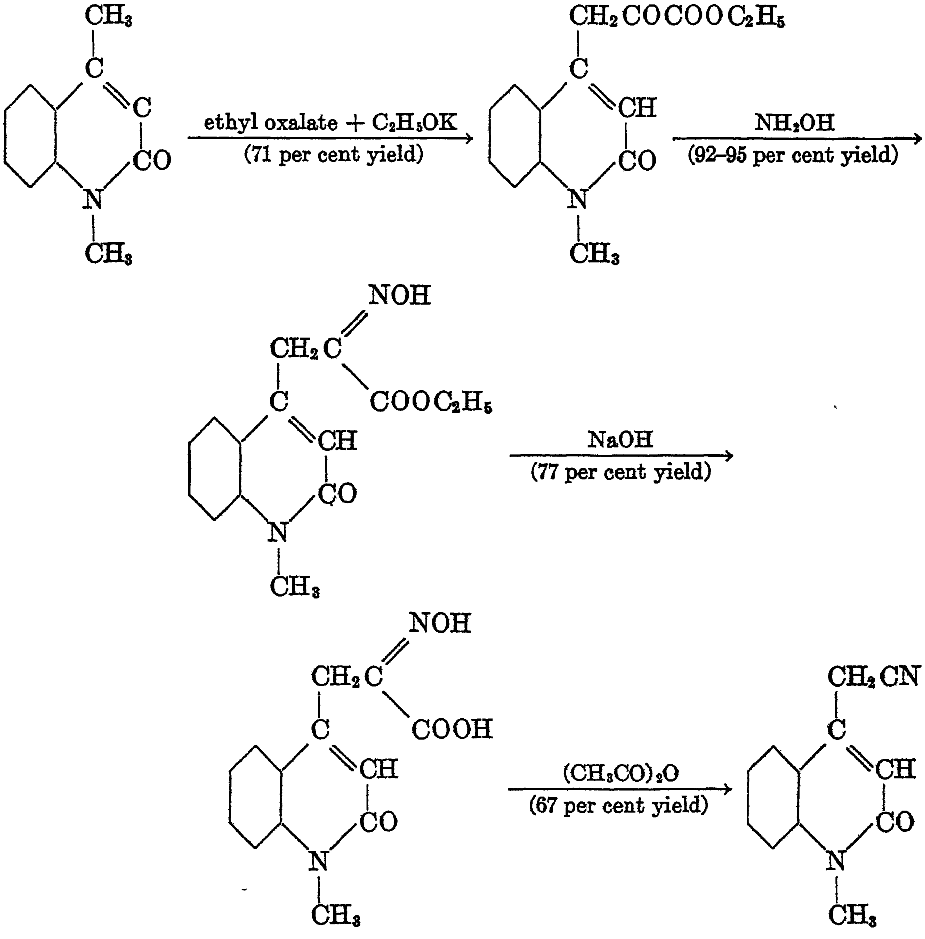


Products of this type when heated or when treated with alkali form the corresponding nitriles in good yield unless the isoxazole ring is stabilized by a substituent in the 3-position.

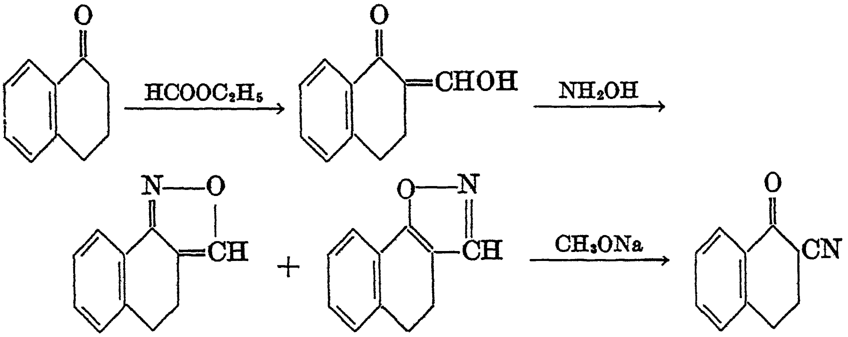
Since the reaction of alkali cyanides and many α-haloketones leads to cyano derivatives of ethylene oxide (see page 205), the methods involving oxime dehydration have been used to prepare previously unavailable β-ketonitriles. By treating the oximinochloride of monoethyl oxalate with sodium salts of active hydrogen compounds, Musante was able to prepare the corresponding isoxazoles. These intermediates, usually not isolated, were converted by hot alcoholic alkali to the nitriles. The reaction is applicable to β-keto esters, cyanoacetic esters, and β-diketones (425).



A similar technique is illustrated for 1,4-dimethylcarbostyryl (305).



A related synthesis involving the formylation of ketones with alkoxides and ethyl formate has been studied by Johnson and Shelberg. Treatment of the β-ketoaldehyde with hydroxylamine gives two isoxazoles. The neutral isomer is inert to the action of sodium methoxide and is easily separated from the ketonitrile which is formed from the reactive isomer. α-Tetralone is converted in 79 per cent over-all yield to its β-cyano derivative, with the concurrent formation of 9 per cent of the neutral isoxazole.



l-Menthone gives 57 per cent ketonitrile and 21 per cent stable isoxazole isomer, while only the nitrile is obtained from camphor. Since the reaction fails completely with cyclopentanone rings, Johnson and Shelberg have suggested that it be used as a basis for proof of structure in sterol chemistry. Even sterically hindered open-chain ketones, such as acetomesitylene, are converted in very high yields to the ketonitriles (298).

The principal side-reaction in the dehydration of oximes is a thermal rearrangement of the Beckmann type which leads to amides and acids. Thus, certain monoöximes of arylglyoxals are converted to acids and hydrogen cyanide (61).

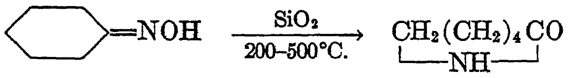
$$\mathrm{ArCOCH{=}NOH \rightarrow ArCOOH + HCN}$$

The formation of amides by rearrangement of oximes is catalyzed by Raney nickel at 80–150°C. (453).

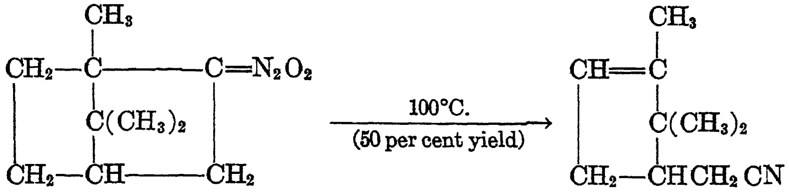
$$\mathrm{RCH{=}NOH \rightarrow RCONH_2}$$

In this manner the appropriate aldoximes are converted to acetamide (86 per cent yield), benzamide (75 per cent yield), furoamide (88 per cent yield), caprylamide (90 per cent yield), and β-phenylpropionamide (30 per cent yield).

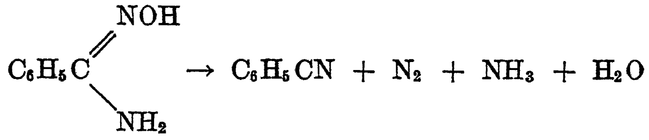
Monoöximes of diketones such as acenaphthenequinone give the cyano acid or the related imide, depending on the reaction conditions (37). Ketoxime pyrolysis may lead to mixtures of various products (282, 321). Under controlled conditions the vapor-phase pyrolysis of cyclohexanone oxime in industrial practice gives high yields of ε-aminocaprolactam, an intermediate for the preparation of polyamide plastics and fibers (355).



A reaction closely related to ketoxime pyrolysis is the transformation of pernitrosocamphor to campholenonitrile (207).



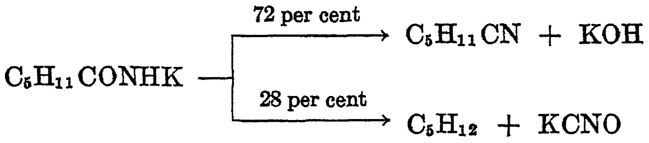
Benzamidoxime is similarly pyrolyzed to benzonitrile (333).



VIII. Dehydration of Amides

A. DEHYDRATION OF AMIDES BY CHEMICAL REAGENTS

In 1832 Wöhler and Liebig distilled benzamide over barium oxide and obtained an oil which was subsequently recognized as benzonitrile, the first nitrile to be synthesized. The use of basic reagents for effecting amide dehydrations has not proved desirable, although pyrolysis of the sodium derivative of benzamide has been reported to give 85 per cent yields of benzonitrile (324). It has also been observed that the potassium derivatives of amides of two to six carbon atoms are converted by heat to the nitriles. Appreciable amounts of by-product hydrocarbon are also formed (40).



$$C_5H_{11}CONHK \xrightarrow{\text{72 per cent}} C_5H_{11}CN + KOH$$
$$C_5H_{11}CONHK \xrightarrow{\text{28 per cent}} C_5H_{12} + KCNO$$

The most useful chemical reagents for effecting the dehydration of amides are without exception the halides or anhydrides of organic or inorganic acids. The use of *phosphorus pentoxide* to dehydrate ammonium salts or amides in both the aliphatic and the aromatic series was introduced by Dumas in 1847 (169).

$$RCONH_2 + P_2O_5 \rightarrow RCN + 2HPO_3$$

Customarily the reaction is carried out by dry distillation of an intimate mixture of the solid amide and finely divided phosphorus pentoxide. Yields are improved if the temperature (usually 100–200°C.) and pressure are adjusted so that the product is distilled from the metaphosphoric acid as rapidly as formed. Stirring of the reaction is often complicated by frothing and by the pasty, semisolid consistency of the mixture. An inert diluent such as sand or mineral oil is often employed to facilitate heat transfer.

In spite of the seemingly drastic conditions and intractable nature of the reaction mixture, the method is exceptionally versatile and provides excellent yields of a large variety of nitriles. Aliphatic monoamides are dehydrated in nearly quantitative yields (309, 329). Substituents such as halo, cyano, nitro, alkoxy, and carbalkoxy groups are not affected, but free hydroxyl or primary or secondary amino groups lead to side-reactions. Aliphatic diamides and polyamides have been successfully converted as, for example, in the classic proof of structure of cyanogen by the dehydration of oxamide (42):

$$NH_2COCONH_2 \xrightarrow{P_2O_5} (CN)_2$$

N,*N*-Dipropyloxamide, however, is converted to the corresponding cyanoformamide in 65 per cent yield (18).

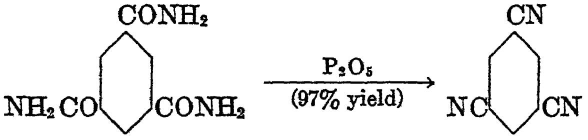
$$(n\text{-}C_3H_7)_2NCOCONH_2 \xrightarrow{P_2O_5} (n\text{-}C_3H_7)_2NCOCN$$

Optically active α-haloamides are not racemized or inverted by this reagent during their conversion to nitriles (41, 529). Olefinic and acetylenic amides are converted smoothly to the corresponding nitriles, some of which are not obtainable by other syntheses. For example, Moureu has obtained the unstable, highly reactive mono- and di-cyanoacetylenes in this manner (411).

$$NH_2COC{\equiv}CCONH_2 \xrightarrow{P_2O_5} CNC{\equiv}CCN$$

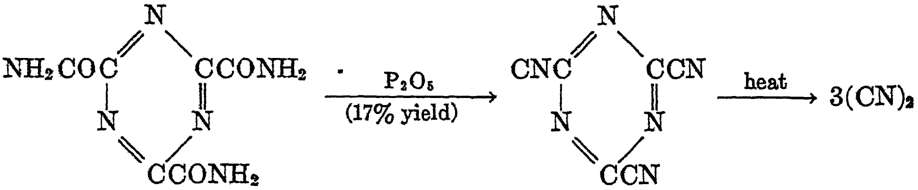
Succinic or maleic amides and their derivatives, however, are converted predominantly to the cyclic imides by loss of ammonia rather than to the dinitrile by dehydration (419, 612). Amides containing acid-sensitive acetal groups are smoothly converted in 75–80 per cent yield to the corresponding nitriles by phosphorus pentoxide in triethylamine solution. Quinoline, *N*-hexylpiperidine, and *N*-ethylmorpholine were less satisfactory solvents (373a).

As would be expected, the reactions of aromatic amides and phosphorus pentoxide give high yields of nitriles. *o*-Diamides have a tendency to form cyclic imides but no difficulty is encountered with polyamides of other configurations such as trimesic amide (38).



Salicylamide, however, forms disalicylamide by intermolecular loss of ammonia when treated with phosphorus pentoxide (135).

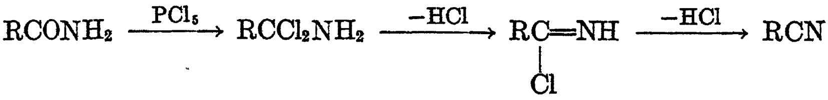
Pyridine-monocarboxamides and -dicarboxamides are smoothly converted to the nitriles by the action of phosphorus pentoxide (339, 347). 1,3,5-Tricyanotriazine, which can be pyrolyzed to cyanogen, is similarly obtained from the triamide (216).



Phosphorus pentasulfide and benzamide are stated to give 40–50 per cent yields of benzonitrile according to the following equation (257):

$$5C_6H_5CONH_2 + P_2S_5 \rightarrow 5C_6H_5CN + 5H_2S + P_2O_5$$

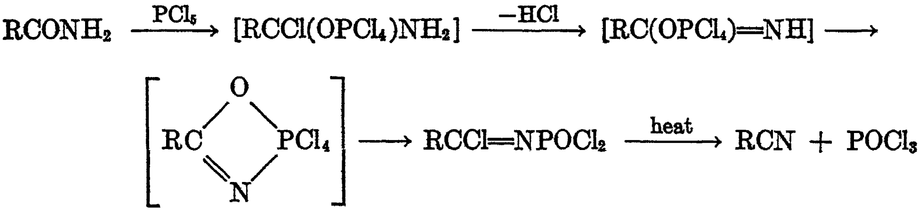
The use of *phosphorus pentachloride* as a reagent for the dehydration of amides was introduced by Gebhart in 1858 (216). Carboxamides were originally thought to be dehydrated through the following mechanism (585):



$$RCONH_2 \xrightarrow{PCl_5} RCCl_2NH_2 \xrightarrow{-HCl} \underset{\displaystyle Cl}{RC}{=}NH \xrightarrow{-HCl} RCN$$

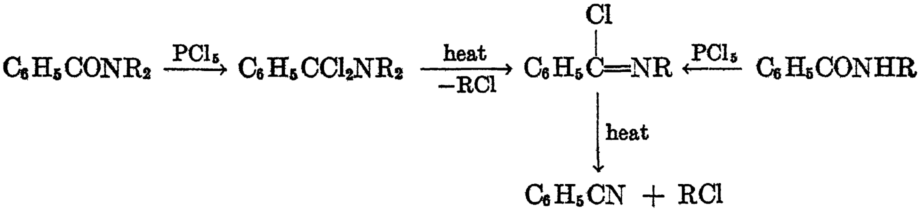
Since carboxamides are thought to exist partially in the imino acid form (21), the unstable amide dichloride is not necessarily an intermediate. Hantzsch prefers to regard the amide dichloride and iminochloride (which may be obtained by the addition of hydrogen chloride to the nitrile) as nitrilium salts, $[RC{\equiv}NH]^+Cl^- \cdot HCl$ and $[RC{\equiv}NH]^+Cl^-$ (240).

The actual precursor of the nitrile is probably a phosphochloride derivative of the iminochloride. This intermediate has been isolated in excellent yield in the trichloroacetamide–phosphorus pentachloride reaction, but it has only a transitory existence in the case of amides of less negatively substituted aliphatic acids. According to von Braun and Rudolph the intermediate is formed by the following mechanism:



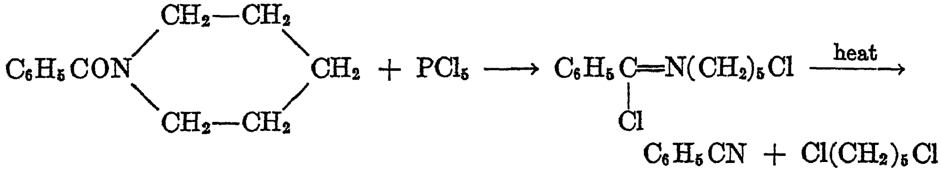
Since this intermediate could not be isolated in the dehydration of the amide by phosphorus oxychloride, it is felt that the previously proposed mechanism involving dehydrochlorination of the iminochloride is erroneous (77).

von Braun has studied the action of phosphorus pentachloride on the amides derived from primary and secondary amines (70, 75). The following transformations have been established for various benzamide derivatives:



$$\begin{tikzcd} C_6H_5CONR_2 \arrow[r, "PCl_5"] & C_6H_5CCl_2NR_2 \arrow[r, "heat", "-RCl"'] & C_6H_5\overset{Cl}{C}{=}NR \arrow[d, "heat"] & C_6H_5CONHR \arrow[l, "PCl_5"'] \\ & & C_6H_5CN + RCl & \end{tikzcd}$$

If *N*-benzoylpiperidine is used, the reaction provides a convenient synthesis of 1,5-dihalides.



A solution of phosphorus pentachloride in *phosphorus oxychloride* has been advocated as a convenient reagent for nitrile dehydration (301, 410). Phosphorus oxychloride alone, however, is especially advantageous for amides containing the hydroxyl and keto groups, since these are not affected by the reagent. Only 30 to 50 mole per cent of the oxychloride is needed for complete conversion to the nitrile. The reaction is thought to proceed by the following mechanism (68, 77):

$$RCONH_2 + POCl_3 \longrightarrow [RCCl(OPOCl_2)NH_2] \xrightarrow{-HCl}$$

$$RC(OPOCl_2){=}NH \xrightarrow{-HOPOCl_2} RCN$$

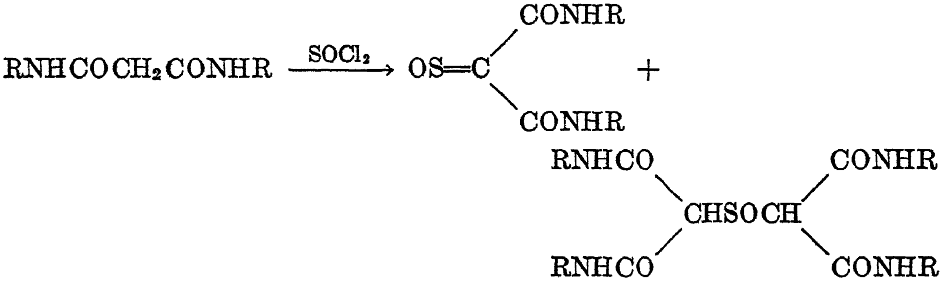
Phosphorus oxychloride is regenerated by one of the following routes:

$$2HOPOCl_2 \rightarrow POCl_3 + HPO_3 + HCl$$

$$3HOPOCl_2 \rightarrow 2POCl_3 + H_3PO_4$$

Benzonitrile and *o*-nitrobenzonitrile are obtained in 95 per cent yield with 25 mole per cent of the oxychloride, but higher ratios are required for equivalent yields of aliphatic nitriles such as lauronitrile or adiponitrile (68). Acetylated amides in the carbohydrate series are converted in 90–95 per cent yields to the corresponding nitriles (348). The addition of sodium chloride to the reaction mixture increases the yield (302, 553). The use of strongly nucleophilic solvents as hydrogen chloride acceptors has proved to be particularly advantageous. Pyridine, dimethylaniline, or other tertiary amines have been recommended (187). Equally good results are claimed for less basic solvents, such as *N*-alkylformanilides (544). These solvents permit the conversion of phthalamide to phthalonitrile, instead of phthalimide which is often formed by acidic dehydrating agents (147, 544).

Thionyl chloride is a popular reagent for the dehydration of amides, since the by-product hydrogen chloride and sulfur dioxide are gaseous and an excess of the volatile reagent is easily removed (400). The reagent fails to dehydrate malonamide, while *N*-substituted malonamides are converted to sulfoxides (428).



Compounds such as α,α-ditosylacetamide (15) and 3-carbamidophthalide (573) are reported to be resistant to dehydration by thionyl chloride, and the reagent causes partial demethylation of mandelamide methyl ether (528). Aromatic sulfonic acids (447) and sulfonyl chlorides (233) are also reported to effect the dehydration of amides in high yields.

$$C_6H_5CONH_2 \xrightarrow{ArSO_3H} C_6H_5CN + H_2O$$

$$C_6H_5CONH_2 \xrightarrow{ArSO_2Cl} C_6H_5CN + ArSO_3H + HCl$$

Anhydrous *aluminum chloride* has been studied as a reagent for amide dehydration. The double salt obtained from equimolar amounts of aluminum chloride and sodium chloride gives better results. The following yields are obtained, using a 10 to 50 per cent molar excess of the double salt: acetonitrile (91 per cent), diphenylacetonitrile (52 per cent), *n*-valeronitrile (63 per cent), benzonitrile (97 per cent), *o*-chlorobenzonitrile (93 per cent), *p*-chlorobenzonitrile (89 per cent), 2,6-dichlorobenzonitrile (67 per cent), *p*-nitrobenzonitrile (20 per cent), α-naphthonitrile (79 per cent), and β-naphthonitrile (80 per cent). Dibasic amides and ammonium salts gave less satisfactory results (437).

Molecular complexes of *boron trifluoride* are effective reagents for amide dehydration (534).

Among the organic acid chlorides, *phosgene* has received considerable attention, probably because of its low cost and availability. Pyridine or other tertiary amines (147, 173) or *N*-alkylformanilides (147) are advantageous nucleophilic solvents for this reaction. The acyl isocyanate has been proposed as an intermediate, since the reaction of benzoyl chloride and potassium isocyanate also gives benzonitrile (405). This has not been confirmed by other evidence.

$$\begin{tikzcd}
C_6H_5CONH_2 + COCl_2 \arrow[dr] & & \\
& {[C_6H_5CONCO]} \arrow[r, "-CO_2"] & C_6H_5CN \\
C_6H_5COCl + KNCO \arrow[ur] & &
\end{tikzcd}$$

Trichloromethyl chloroformate, obtainable by the photochemical chlorination of methyl formate, is a satisfactory dehydrating reagent (259).

3,5-Dinitrobenzoyl chloride in pyridine solution has been proposed as a reagent for the quantitative determination of amides. The hydrogen chloride liberated is titrated to determine the amount of nitrile formed (405).

Benzotrichloride has been used as a reagent for the dehydration of aromatic and aliphatic amides. The reaction temperature may be lowered from 200° to 100°C. by the use of traces of the chlorides of zinc, aluminum, or iron (276).

Acetic anhydride is the most popular of the organic anhydrides for amide dehydration (68). The reaction is reversible. At equilibrium acetamide is 83 per cent converted to the nitrile at 98°C. (87 per cent at 78°C.) by an equimolar quantity of acetic anhydride.

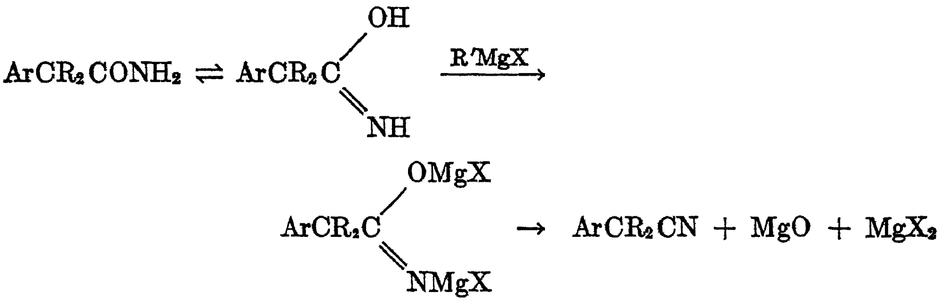
$$CH_3CONH_2 + (CH_3CO)_2O \rightleftharpoons CH_3CN + 2CH_3COOH$$

The distribution of products from 1 mole of benzamide and 1 mole of acetic anhydride was observed to be as follows at equilibrium (330):

$$\underset{(0.48\ \text{mole})}{C_6H_5CONH_2} + \underset{(0.48\ \text{mole})}{(CH_3CO)_2O} \rightleftharpoons \underset{(0.38\ \text{mole})}{C_6H_5CONHCOCH_3} + \underset{(0.66\ \text{mole})}{CH_3COOH} + \underset{(0.14\ \text{mole})}{C_6H_5CN}$$

Traces of cobalt, copper, nickel, molybdenum, and zinc salts are effective catalysts in promoting this reaction, and high conversions may be attained by distilling the acetic acid from the reaction mixture as formed (325, 419, 532).

Trisubstituted acetamides react with aliphatic *Grignard reagents* to give mixtures of ketones and nitriles. The latter predominate if the reagent is an arylacetamide. The following mechanism has been proposed (473):



Aryl Grignard reagents give relatively larger amounts of the ketone, but the *tert*-butyl Grignard reagent leads to a 73 per cent yield of pivalonitrile from the corresponding amide (594).

B. DEHYDRATION OF AMIDES BY CATALYTIC METHODS

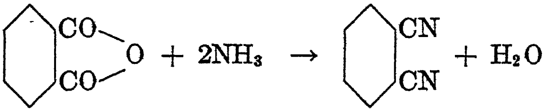
It has long been known that compounds such as ammonium acetate or acetamide will be dehydrated if heated strongly. However, in the absence of catalysts the conversion is low and considerable quantities of the acid and ammonia are regenerated through hydrolysis of the amide by the water liberated in the principal reaction. For example, distillation of stearamide at atmospheric pressure gives 33 per cent stearic acid, 30 per cent stearonitrile, and 5 per cent unchanged stearamide (471). Similarly, distillation of sebacic diamide gives predominantly 9-cyanononoic acid (45). It was observed by Boehner in 1916 that if acetamide were refluxed at 250–260°C. over alumina, lamp black, pumice, or silica improved yields (65–68 per cent) of acetonitrile were obtained. Still better results were obtained if the reaction was carried out in the vapor phase at 420°C. Under these conditions a pumice catalyst gave a 91 per cent yield (54).

Conditions similar to the above are now used for the large-scale commercial production of hydrogen cyanide (and sodium cyanide) from formamide. The amide vapors are passed over catalysts such as aluminum phosphate at 350–370°C. and absorbed in aqueous alkali (371). Acrylamide and methacrylamide are dehydrated in 67–75 per cent yields to the corresponding nitriles at 490°C.

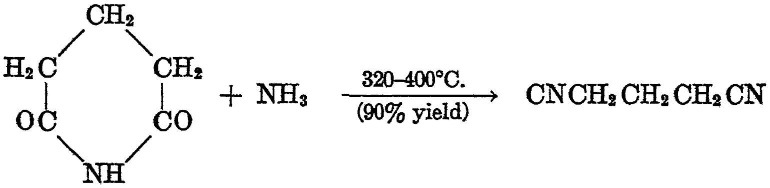
over fused manganese dioxide. Reduced pressures contribute toward the attainment of high yields (342).

At the same time that Boehner was investigating the catalytic dehydration of amides, Reid announced a similar synthesis in which the acid and ammonia are passed in the vapor phase over dehydration catalysts to give the nitrile directly without isolation of the intermediate ammonium salt or amide (572). When acetic acid and an excess of ammonia are passed at 500°C. over a catalyst of thoria or alumina supported on pumice, an 85 per cent yield of acetonitrile is obtained. Silica gel as a catalyst at 500–525°C. gives 95 per cent yields (406). The following nitriles were similarly obtained in the yields indicated: propionitrile (85 per cent), *n*-butyronitrile (90 per cent), *n*-valeronitrile (80 per cent), isovaleronitrile (94 per cent), capronitrile (90 per cent), heptonitrile (93 per cent), lauronitrile (55 per cent), phenylacetonitrile (87 per cent), and β-phenylpropionitrile (81 per cent).

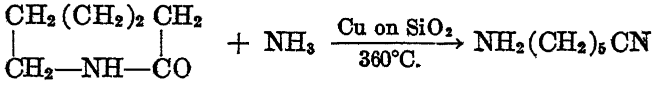
A liquid-phase technique for aliphatic monobasic or dibasic acids involves blowing ammonia into the molten acid at elevated temperatures. Amide formation occurs above 100°C. and nitrile formation occurs in the 200–350°C. range. Of numerous catalysts mentioned for the latter step about 2–5 per cent of phosphoric acid appears to be the most popular. This technique has been employed for the production on a commercial scale of long-chain fatty acid nitriles (472) and adiponitrile (189). With phthalic acid the liquid-phase technique, however, leads to the production of phthalimide rather than phthalonitrile. The latter is obtained at higher temperatures (350–500°C.) in the vapor phase over various dehydration catalysts (365).



A relatively short contact time (2–5 sec.) and an eight- to ten-fold excess of ammonia enable yields of 80–90 per cent to be obtained. Lower temperatures favor higher amounts of phthalimide formation, while higher temperatures lead to increasing amounts of benzonitrile, which arises through decarboxylation (365, 419). Phthalimide undergoes the reaction as readily as phthalic anhydride, and glutarimide is similarly converted to glutaronitrile (382).



ε-Aminocaprolactam is similarly converted to ε-aminocapronitrile (355).



Other catalysts that have been recommended for vapor-phase dehydration of amides are Japanese acid clay (314), sulfates, phosphates, borates, and molybdates of aluminum, boron, vanadium, beryllium, and zirconium (16a, 279).

Another variation involving the simultaneous preparation and dehydration of amides was introduced by Maihle, who passed ammonia and carboxylic esters over dehydration catalysts at elevated temperatures.

$$\mathrm{RCOOR'} + \mathrm{NH_3} \xrightarrow[500^\circ\mathrm{C.}]{\mathrm{Al_2O_3}} \mathrm{RCN} + \mathrm{R'OH} + \mathrm{H_2O}$$

The by-product alcohol is often converted to the corresponding ether or olefin. The reaction has been applied to both the aliphatic and the aromatic series, the yields being somewhat better in the latter case.

Unsaturated nitriles such as crotononitrile, oleonitrile, and cinnamonitrile have also been prepared in this manner. A nearly quantitative yield of hydrogen cyanide is reported to be obtained from the reaction of carbon monoxide and ammonia at 400°C. Alumina and thoria are the preferred catalysts. Primary aliphatic amines may be substituted for ammonia as a nitrogen source.

$$\mathrm{RCOOR'} + \mathrm{R''CH_2CH_2NH_2} \xrightarrow{-\mathrm{R'OH}}$$
$$[\mathrm{RCONHCH_2CH_2R''}] \rightarrow \mathrm{RCN} + \mathrm{R''CH{=}CH_2} + \mathrm{H_2O}$$

Acid chlorides may be substituted for esters in this method of nitrile synthesis (378).

The use of nickel catalysts causes a side-reaction reminiscent of the Hofmann degradation. Aromatic esters are degraded to the aromatic amines, but the corresponding aliphatic amines usually undergo dehydrogenation to the lower nitriles (377).

$$\mathrm{ArCOOR} + \mathrm{NH_3} \xrightarrow{\mathrm{Ni}} \mathrm{ArNH_2} + \mathrm{CO} + \mathrm{ROH}$$

$$\mathrm{RCH_2COOR'} + \mathrm{NH_3} \xrightarrow{\mathrm{Ni}} [\mathrm{RCH_2NH_2}] \rightarrow \mathrm{RCN} + \mathrm{H_2}$$

Methyl iminobenzoate is converted to benzonitrile by heating at 250–280°C. for 26 hr. The trimer of benzonitrile, cyaphenine, may be the intermediate in this reaction (296, 604).

IX. MISCELLANEOUS SYNTHESES

A large number of nitrile syntheses have been proposed which involve heating an acid or one of its derivatives with some nitrogen-containing compound. Only those methods will be mentioned in this section which have preparative value or are of theoretical interest.

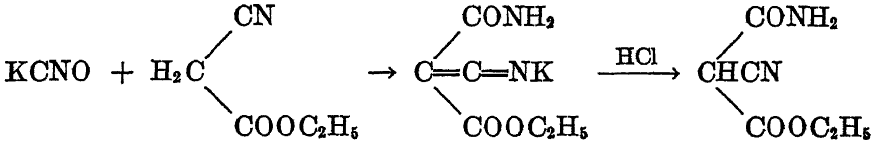
Schiff observed in 1857 that the reaction of benzoyl chloride with potassium cyanide gave some benzonitrile (512). The fusion of an aromatic acid with potassium thiocyanate was introduced by Letts in 1872 as a preparative method (357). It was subsequently observed that Letts's method gave better yields if lead thiocyanate was employed (334). A systematic study of the reaction by

Reid has shown that dry distillation of the zinc salt of the acid with a 20 per cent excess of lead thiocyanate gives the best yield of benzonitrile (86 per cent conversion and 91 per cent yield), although lead, barium, or potassium ferrocyanide, lead cyanate, and silver cyanide all give yields in excess of 50 per cent. The reaction fails with amino-, nitro-, or hydroxy-benzoic acids.

$$(C_6H_5COO)_2Zn + Pb(CNS)_2 \rightarrow 2C_6H_5CN + PbS + ZnS + 2CO_2$$

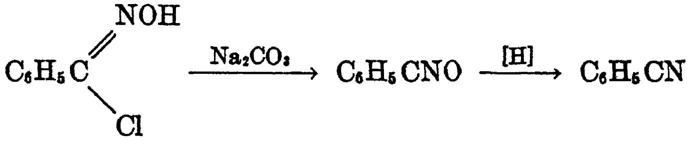
In the aliphatic series the yields are poorer. Several metallic salts of acetic acid were investigated. Manganese and zinc acetates are converted by lead thiocyanate to acetonitrile in 70 per cent and 46–57 per cent yields, respectively. Yields of 16 to 29 per cent are obtained from the acetates of cobalt, strontium, barium, copper, and lead, while the use of magnesium, nickel, tin, and iron salts gives definitely inferior results (572).

Potassium cyanate reacts with the reactive methylene group of cyanoacetic ester in a different fashion, but this type of synthesis does not appear to have been investigated further (197).



$$KCNO + H_2C\begin{matrix}\diagup CN \\ \diagdown COOC_2H_5\end{matrix} \rightarrow C\begin{matrix}\diagup CONH_2 \\ \\ \diagdown COOC_2H_5\end{matrix}\!\!=C=NK \xrightarrow{HCl} CHCN\begin{matrix}\diagup CONH_2 \\ \\ \diagdown COOC_2H_5\end{matrix}$$

Nitrile oxides which are obtained by dehydrochlorination of hydroxamic chlorides can be reduced with zinc and acetic acid to the nitriles (597).

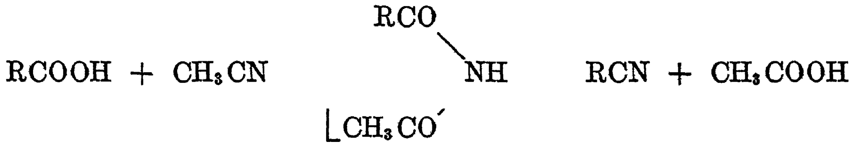


$$C_6H_5C\begin{matrix}\nearrow\!\!\!\!\!\diagup NOH \\ \diagdown Cl\end{matrix} \xrightarrow{Na_2CO_3} C_6H_5CNO \xrightarrow{[H]} C_6H_5CN$$

In a somewhat related reaction dithio acids and hydroxylamine hydrochloride in pyridine solution give rise to aliphatic nitriles directly. In the aromatic series aldoximes are formed (617).

$$RCSSH + NH_2OH \rightarrow RCN + H_2S + H_2O + S$$

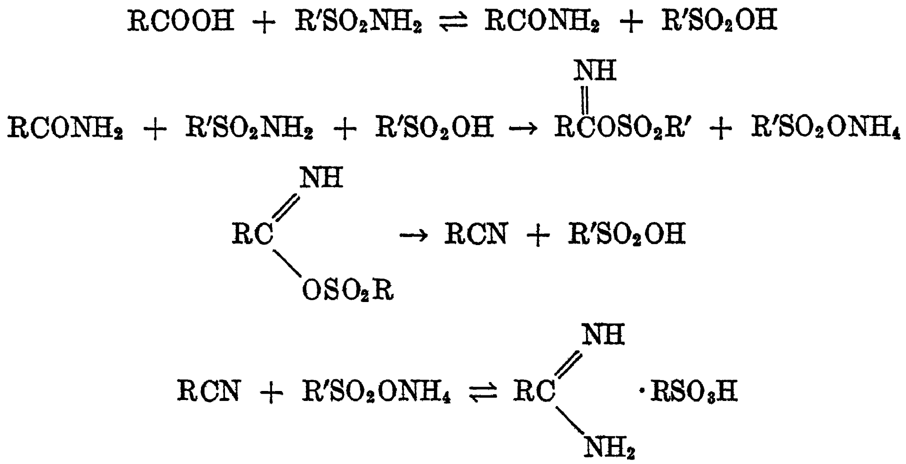
A nitrile interchange reaction between excess acetonitrile and a higher acid takes place at 250–300°C. under pressure. Acidic substances act as catalysts and the mechanism undoubtedly involves the mixed imide as an intermediate (368).



$$RCOOH + CH_3CN \qquad \begin{matrix} RCO\diagdown \\ NH \\ \llcorner CH_3CO\diagup \end{matrix} \qquad RCN + CH_3COOH$$

Aliphatic acid chlorides are converted by acetonitrile in the presence of aluminum chloride to the corresponding nitrile (431a).

A synthesis of considerable utility which involves the fusion of an acid with benzenesulfonamide was introduced by Remsen in 1896 (485, 496). This reaction has been studied in considerable detail recently by Oxley and coworkers, who have shown that the mechanism involves the following sequence of reactions. Under slightly modified conditions the amidines may be obtained as the principal reaction products.



$$\mathrm{RCOOH + R'SO_2NH_2 \rightleftharpoons RCONH_2 + R'SO_2OH}$$

$$\mathrm{RCONH_2 + R'SO_2NH_2 + R'SO_2OH \rightarrow R\overset{\overset{NH}{\|}}{C}OSO_2R' + R'SO_2ONH_4}$$

$$\mathrm{RC}\begin{matrix}\diagup\!\!\!\diagup \mathrm{NH}\\ \diagdown \mathrm{OSO_2R}\end{matrix} \rightarrow \mathrm{RCN + R'SO_2OH}$$

$$\mathrm{RCN + R'SO_2ONH_4 \rightleftharpoons RC}\begin{matrix}\diagup\!\!\!\diagup \mathrm{NH}\\ \diagdown \mathrm{NH_2}\end{matrix}\cdot\mathrm{RSO_3H}$$

With 2 moles of benzenesulfonamide at 220°C. ± 10° in 1 or 2 hr. the following conversions of acids to nitriles are obtained: benzonitrile (90 per cent), *o*-nitrobenzonitrile (11 per cent), *p*-nitrobenzonitrile (81 per cent), 2,4-dinitrobenzonitrile (79 per cent), *p*-chlorobenzonitrile (66 per cent), 2,4-dichlorobenzonitrile (80 per cent), *o*-cyanophenyl methyl sulfone (83 per cent), *m*-cyanophenyl methyl sulfone (61 per cent), *p*-cyanophenyl methyl sulfone (75 per cent), *p*-cyanophenyl phenyl sulfone (74 per cent), *p*-anisonitrile (10 per cent), di-*p*-cyanophenyl ether (45 per cent), phenylacetonitrile (22 per cent). The reaction fails with chloroacetic, oxalic, malonic, tartaric, salicylic, *o*-anisic, *p*-hydroxybenzoic, anthranilic, and *p*-aminobenzoic acids (447).

Fusion of phospham with aliphatic acids is stated to give the nitriles (574).

$$\mathrm{2RCOOH + PN_2H \xrightarrow{150\text{–}200°C.} 2RCN + H_3PO_4}$$

Dicyandiamide (143) and urea (46) have been proposed as convenient nitrogen sources for the conversion of acids to their nitriles.

Phenylhydrazones of aldehydes are converted to nitriles by pyrolysis at 180–200°C. in the presence of catalytic amounts of the chlorides of copper, lead, or zinc.

$$\mathrm{RCH{=}NNHC_6H_5 \rightarrow RCN + C_6H_5NH_2}$$

The lower aliphatic aldehydes lead principally to derivatives of indole, but yields of nitriles increase with higher molecular weight. Isobutyronitrile and isoheptanonitrile are obtained in 37 per cent and 60 per cent yields from their respective aldehyde phenylhydrazones (14).

The pyrolysis of Schiff bases also leads to nitriles. The reaction is conducted in the vapor phase at 420°C. over finely divided nickel. From *N*-ethylbenzaldimine are obtained principally benzonitrile and ethane, although appreciable quantities of toluene and acetonitrile are also obtained (379).

$$C_6H_5CH{=}NC_2H_5 \rightarrow C_6H_5CN + C_2H_6\ (+\ C_6H_5CH_3 + CH_3CN)$$

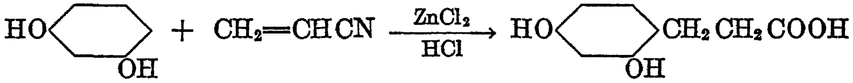
Benzaldehyde may also be converted to benzonitrile through the action of a benzene solution of hydrazoic acid in the presence of dry hydrogen chloride (514).

$$C_6H_5CHO + HN_3 \xrightarrow{HCl} C_6H_5CN + H_2O + N_2$$

The scope of this review has been limited to those reactions in which the cyano group is formed or introduced into an existing organic nucleus. However, brief mention should be made of recently developed techniques for the introduction of the cyanoethyl group according to the general reaction:

$$RH + CH_2{=}CHCN \rightarrow RCH_2CH_2CN$$

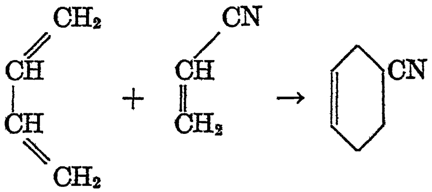
The reaction is effected by traces of alkaline catalysts under mild conditions. Alcohols, amines, mercaptans, and related compounds lead to the corresponding β-substituted propionitriles. Bruson has found that in the case of compounds containing reactive carbon–hydrogen bonds a true carbon synthesis of the Michael type is effected. Thus, hydrocarbons such as fluorene, cyclopentadiene, and indene (87), chlorinated hydrocarbons such as chloroform (90), and nitro compounds such as nitromethane (91) are cyanoethylated in good yield. Other compounds having reactive hydrogens in the α-position, such as esters (88, 317), nitriles (91), ketones (91), aldehydes (92) and sulfones (92), easily add one or more molecules of acrylonitrile. Reactive aromatic hydrocarbons such as resorcinol react similarly in the presence of acidic catalysts (351).



Acrylonitrile and its derivatives are conveniently attached to aromatic groups by reaction with diazonium halides (316, 388, 421).

$$ArN_2Cl + CH_2{=}CHCN \xrightarrow{-N_2} ArCH_2CHClCN \xrightarrow{-HCl} ArCH{=}CHCN$$

Another technique for the introduction of cyanoethyl or dicyanoethyl groups into a molecule involves the Diels–Alder condensation of 1,3-dienoic compounds with acrylonitrile, fumaronitrile, and their derivatives (416, 438).



X. Toxicity of Hydrogen Cyanide and Nitriles

Insofar as hydrogen cyanide and its derivatives are commonly employed in the synthesis of nitriles, a few observations on the toxicity and physiological action of these compounds should be of interest.

A single dose of 50 mg. of hydrogen cyanide may be fatal to a human being, although a great difference in individual susceptibility exists. For example, it has been reported that an attempt to poison Rasputin in 1916 by placing a large overdose of potassium cyanide in his wine failed because he had an alkaline stomach condition caused by acute alcoholic gastritis. Since rats, fed nine times the lethal dose of sodium cyanide, will recover if glucose and colloidal sulfur are injected intravenously, it would be reasonable to assume that diabetics would also be less susceptible to cyanide poisoning.

The average chemist, however, must rely on careful manipulative technique and adequate ventilation. Hydrogen cyanide has a distinctive odor. It is more easily detected while smoking, because of the disagreeable acrid taste it leaves in the mouth. The warning afforded by the sense of smell is not durable, however, since the olfactory nerves are rapidly paralyzed. Death by asphyxiation often occurs in a relatively short time. This is caused by paralysis of the central nervous system through inhibition of a single enzyme, cytochrome oxidase (40a) rather than by the accumulation of cyanohemoglobin in the blood stream, as has been commonly supposed.

The following lethal concentrations of hydrogen cyanide in air for human beings are cited by Fabre (176a):

Instantly fatal	0.3 mg. per liter
Fatal in 30 to 60 min	0.12–0.15 mg. per liter
Fatal after several hours	0.02–0.04 mg. per liter
Tolerable for 6 hr.	0.01 mg. per liter

Supposedly, hydrogen cyanide poisoning is not cumulative and the spell passes quickly in fresh air. Actually, repeated sublethal exposures leave lesions of the central nervous system leading to difficulty of speech, paralysis, anemia, vertigo, heart trouble, and larynx trouble.

Recommendations for the treatment of cyanide poisoning have been made by Chen, Rose, and Clowes (109). These include inhalation of amyl nitrite as a preliminary adjuvant, alternate intravenous injection of solutions of sodium nitrite and sodium thiosulfate, and artificial respiration if necessary to restore breathing. The use of *p*-aminopropiophenone and sodium thiosulfate is equally effective. It is recommended that pearls of amyl nitrite be kept in the laboratory and that a kit containing ampoules of sterile solutions of sodium nitrite and sodium thiosulfate and syringes be kept at a nearby first aid station.

Cyanogen, cyanogen halides, and certain nitriles are almost as toxic as hydrogen cyanide. In general, the saturated aliphatic and aromatic nitriles are no more toxic than many chemicals commonly regarded as relatively harmless. Unsaturated nitriles, cyanohydrins, and α-aminonitriles, however, approach hydrogen cyanide in toxicity. Halogenated nitriles are also quite toxic and some are extremely lachrymatory. Unsaturated nitriles, such as acrylonitrile and fumaronitrile, cause extensive and painful dermatitis when the liquid, dust, or vapors are brought in contact with the skin. In general, the mechanism and symptoms of poisoning by nitriles are similar to those caused by hydrogen cyanide. Table 6 indicates the relative toxicity of some of these materials.

A concentration of 20 p.p.m. of acrylonitrile in the atmosphere of industrial plants has been recommended as a maximum (167).

XI. CONCLUSION

In the preceding review an attempt has been made to describe the principal techniques which are available for the synthesis of nitriles. Specific procedural details have been omitted, since these may easily be obtained from original sources. However, the scope, limitations, and postulated reaction mechanisms of each reaction have been presented as a guide to chemists who are confronted with the choice of a method for specific synthetic problems.

TABLE 6

Toxicity of nitriles

COMPOUND	MEDIAN LETHAL DOSE	DOSAGE METHOD	TEST ANIMAL	REFERENCE
	grams/kilogram			
HCN	0.006	Oral	Mouse	(214)
$CNCOOCH_3$	*ca.* 0.01	Inhalation	Mouse	(190)
CH_3CN	2.65	Intravenous	Rabbit	(153)
CH_3CH_2CN	1.08	Intravenous	Rabbit	(153)
$CH_2{=}CHCN$	0.085	Intravenous	Rabbit	(153)
$CH{\equiv}CHCN$	0.0147	Intravenous	Rabbit	(153)
$CH_3CH_2CH_2CN$	0.98	Intravenous	Rabbit	(153)
$CH_2{=}CHCH_2CN$	0.06	Intravenous	Rabbit	(153)
$C_6H_5CH_2CH_2CN$	0.039	Intravenous	Rabbit	(153)
$C_6H_5CH{=}CHCN$	0.034	Intravenous	Rabbit	(153)
$C_6H_5C{\equiv}CCN$	0.01	Intravenous	Rabbit	(153)
$C_5H_{11}C{\equiv}CCN$	0.19	Intravenous	Rabbit	(153)
$CNC{\equiv}CCN$	0.195	Intravenous	Rabbit	(153)
$RCH(NH_2)CN$	0.02–0.16		Rabbit	(509)
$C_5H_{11}CN$	0.31	Subcutaneous	Guinea pig	(153)

In general, the aliphatic nitriles are most conveniently prepared from alkyl halides or sulfates by metathesis reactions with alkali cyanides. With alicyclic, secondary, and tertiary halides, it may be preferable to employ the Grignard reagent and cyanogen or cyanogen chloride. If the requisite aldehyde or acid is available, the procedures involving oxime and amide dehydration are to be recommended.

A comparison of various laboratory techniques for the preparation of aromatic nitriles was made by Tingle in 1906 (564). In the preparation of benzonitrile the following yields were recorded: Sandmeyer reaction from aniline (64 per cent), phosphorus pentoxide dehydration of benzamide (95 per cent), modified Letts reaction of benzoic acid and lead thiocyanate (71 per cent), fusion of sodium benzenesulfonate and potassium cyanide (26 per cent). Subsequent developments have improved some of the above yields and provided other methods that are to be recommended. These include the Rosenmund–von Braun reaction of halides and copper cyanide, the Friedel–Crafts–Karrer cyanogenation of hydrocarbons with cyanogen chloride and aluminum chloride, and the fusion of acids with benzenesulfonamide.

Acyl or aroyl cyanides are best obtained by metathesis reactions of the acid halides with copper or pyridinium cyanide or from methyl ketones through dehydration of the oximino derivative with acetic anhydride.

XII. References

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CURARIFORM ACTIVITY AND CHEMICAL STRUCTURE

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I. INTRODUCTION

It has been known for many years that the material called curare has the effect of causing muscular paralysis when injected into frogs or mammals. This material had been brought from South America to Europe in small quantities by explorers, and was known to have been prepared by the natives in the form of aqueous extracts and concentrates for use as an arrow poison. The samples available for scientific examination have varied so widely in botanical origin, physiological potency, and chemical constitution that it is only in recent years that definite information has been obtained about the chemical compounds responsible for the "curare activity" of the South American curare.

The physiological effect of curare (curare or curariform activity) has been found to have useful applications in surgery and in the treament of spastic and other paralytic conditions. Furthermore, a large number of synthetic and naturally occurring organic compounds have been studied which have physiological effects similar to, although in practically all cases less intense than, the active materials present in South American curare.

The object of the present paper is to review the literature and to tabulate the compounds which have been reported to exhibit curare or curare-like activity in order to deduce, if possible, what units of chemical structure are responsible for, enhance, or reduce this activity. Other types of physiological actions which frequently accompany curare activity have been recorded.

II. HISTORICAL

The paralyzing action of curare has been known for centuries. The first record of the primitive use of curare is in Hakluyt's description of Sir Walter Raleigh's contact with Indians of the Orinoco in 1595. Watterton and Brodie in 1815 demonstrated that death from curare was due to respiratory failure. Bernard in 1844 first described the location of the physiological action of curare as being at the junction of the nerve and muscle (myoneural junction). The paralytic action of curare led to its early investigation in causing relaxation of muscles in such convulsive conditions as epilepsy, rabies, tetanus, strychnine poisoning, and various tics. The non-homogeneity of the crude curare preparations made physiological investigations and clinical use difficult, with the result that chemical investigations were started (8, 74).

The chemical examination of curare preparations was first carried out in 1829 by Roulin and Boussingault (187), who isolated a syrupy mass which they called curarine. In the period following, Buchner (18), Preyer (158), Sachs (188), and other workers isolated amorphous alkaloids for which they proposed various structures. Boehm (12) brought some order into the curare field when he showed that the South American curare preparations were of three kinds, distinguished by the type of container in which they were packed. They were (*a*) para, tube, or bamboo curare, packed in bamboo tubes, (*b*) pot curare, exported in small earthenware pots, and (*c*) gourd or calabash curare, packed in small gourds. Furthermore, Boehm showed that curare preparations contained several alkaloids of two general types: amorphous quaternary bases which produced the curare action, and tertiary bases which were inactive. The constitution of the various curare preparations depended on the botanical origin, which not only differed among the three types of curare but also differed from sample to sample of the same type. Curare was first believed to be prepared from South American *Strychnos* species, but later chemical evidence indicated that the alkaloids also occur in menispermaceous plants (86).

King (129) isolated the first crystalline active alkaloid, *d*-tubocurarine chloride, from tube curare, and found that a dose of 0.5 mg./kg. produced complete curare paralysis of frogs, as compared to doses of 2.5–5 mg./kg. required of various curare preparations. He (129, 130) was able to show that *d*-tubocurarine chloride was a diquaternary base with a bisbenzyltetrahydroisoquinoline type structure (see Section IV,D,1 on page 351 *et seq.* for the chemistry of the curare alkaloids). King's chemical evidence (131) indicated that there was a close relationship between the alkaloids of pot and tube curare.

More recently, Wintersteiner and Dutcher (223) isolated *d*-tubocurarine chloride from a sample of South American curare which was known to have been prepared from only one plant species, *Chondodendron tomentosum* Ruiz and Pavon. This gave a source of a pure, active curare alkaloid and of standardized curare preparations, so that physiological and clinical investigations could be carried out with a greater degree of certainty.

Investigations of gourd curare have not been as extensive as those of the other types. Wieland and coworkers (217–220) isolated a group of very active quaternary alkaloids from gourd curare, which have been shown by preliminary examination to be different in chemical nature from the other curare alkaloids (see Section IV,D,1). Although these alkaloids are very active physiologically, some even more active than *d*-tubocurarine, no reports of any investigations as to their possible therapeutic value were found.

III. CURARIFORM ACTIVITY

A. PHYSIOLOGICAL ASPECTS

Since Bernard's discovery of the peripheral location of the action of curare, many investigations as to the mechanism of curare action have been carried out. It is generally agreed that the curare action is one of prevention, in some manner, of the transfer of impulses from the nerve to the muscle at the myoneural junction.

The most widely accepted theory for the mechanism of neuromuscular transmission is the acetylcholine theory, which states that an impulse from the nerve causes the formation of acetylcholine which in turn causes stimulation of the muscle. The acetylcholine formed by each impulse is quickly hydrolyzed by cholinesterase, and the process, which takes place at the myoneural junction, is repeated for each impulse of the nerve. Rosenblueth and coworkers (186a, 210) postulated that there is a range of concentrations of acetylcholine to which the muscle responds. Response by the muscle does not occur if the concentration is below the "threshold of excitation" or above the "upper paralytic boundary". This postulate explains why the injection of acetylcholine or drugs that are known to inhibit the action of cholinesterase cause curare-like paralysis, since the acetylcholine would be present in concentrations above the upper paralytic boundary. Because curare does not interfere with the liberation of acetylcholine and does not inhibit the action of cholinesterase, they believed that the action of curare was one of raising the threshold of excitation of the muscle. Thus, it is postulated that although the usual amount of acetylcholine is produced by the impulse from the nerve, it is not enough to cause response by the muscle.

The peripheral paralysis due to curare occurs in a definite order, so that the first signs of curare poisoning are dropping of the eyelids, drowsiness, loss of speech, and paralysis of the neck muscles. The extremities are then affected, followed by the muscles of the diaphragm; finally, death occurs from respiratory failure. A compound which produces a true curariform action has no effect on the central nervous system or the heart. Reflexes are diminished but not abolished, and a paralyzed muscle returns to its normal state without showing any harmful effects. That death occurs from respiratory failure before other toxic manifestations are noted has been shown by giving dogs up to fifty times the ordinary lethal dose of a curare preparation without fatality by maintaining artificial respiration (8, 74).

The nature of the action of curare led to early investigations as to the possible therapeutic use in treatment of various neuromuscular disorders. Some success has been attained in the use of curare for relaxation of muscles during surgery and for treatment of various convulsive states. The difficulties encountered because of non-homogeneity of preparations have been alleviated by the availability of purified, standardized preparations; however, the margin of safety is still low. Another disadvantage has been that it is ineffective orally (8, 86). Because of these difficulties, many other compounds which produce a curare-like effect have been investigated clinically, the most notable being certain erythrina alkaloids. Erythroidine and dihydro-β-erythroidine, the two erythrina alkaloids which have been used extensively, have shown considerable promise as therapeutic agents, particularly because they are effective orally (20, 57). Their main disadvantage is that they do not have as intense and prolonged an action as the curare alkaloids (19, 20).

Since the known drugs exhibiting curariform activity have certain disadvantages, it was hoped that a literature survey would furnish chemical information that could be used in preparing new drugs or improving old ones.

B. TYPES OF COMPOUNDS EXHIBITING CURARIFORM ACTIVITY

Since the active curare alkaloids were quaternary, Brown and Fraser (15, 16) in 1868 attributed curariform action to the onium ion. Since that time many quaternary salts have been investigated, and it has been found that quaternary ammonium, sulfonium, phosphonium, arsonium, and stibonium salts all possess curare activity (5, 32, 102). The onium salts in the order of decreasing intensity of curare action are as follows (167):

$$(CH_3)_4N^+ > (CH_3)_3S^+ > (CH_3)_4P^+ > (CH_3)_4As^+ > (CH_3)_4Sb^+$$

Actually, the ammonium, potassium, and sodium ions and ions of other alkali metals have been shown to exhibit curare activity in varying degrees (5, 32). Attempts have been made, though with little success, to relate quantitatively the intensity of the curare action with the size (5, 117) and the mobility (167) of the cation, since it was the ionic nature of the material which seemed to be essential for the physiological action.

Folkers and Major (57) isolated an active principle, which they called β-erythroidine, from an extract of the seeds of *Erythrina americana* Mill., which had been known for some time to possess curare activity. Subsequent chemical investigations showed that this compound contains a tertiary nitrogen instead of a quaternary nitrogen. This was the first example of a tertiary nitrogen compound that exhibited a marked curare action and, as stated above, the action was of such a nature that the drug has been used clinically rather extensively.

During a systematic investigation of the pharmacological properties of α-glycerol ethers, Berger and Bradley (9) in 1946 observed that certain of the compounds produced paralysis and marked muscular reaction. Further investigations of the most effective of these ethers, α-(*o*-tolyl)glycerol ether, showed that while the action was partially curare-like, it was mostly a depressant action in the spinal cord (9, 10). However the net effect, muscular paralysis, was the same, and this type of compound was proposed as a curare substitute.

C. OTHER PHYSIOLOGICAL ACTIONS FREQUENTLY ACCOMPANYING CURARIFORM ACTIVITY

Hunt and coworkers (99–116) and Renshaw and coworkers (163–183) published a series of papers on onium compounds and their effect on the autonomic nervous system. They attributed three general types of action to quaternary ammonium compounds: curare action, muscarinic action, and nicotinic action.

A muscarinic action is one of direct stimulation of smooth muscles, which is manifest in mammals by slowing of the heartbeat, depression of the blood pressure, vasodilatation, miosis, bronchial constriction, salivation, and sweating (74). Renshaw (163) and Hunt (101, 102) used as a criterion for muscarinic activity the production of a fall in blood pressure which was prevented by atropine, the latter being a specific antagonist to muscarinic activity.

A nicotinic action consists of a primary transient stimulation and a secondary more persistent depression of all sympathetic and parasympathetic ganglia. Thus, the first signs of a nicotinic action are a rise in blood pressure due to peripheral vasoconstriction, followed by a falling of the blood pressure due to vasomotor paralysis. In the stage of paralysis, nicotine thus manifests a curare-like paralysis which largely explains the fact that death from nicotine is due to respiratory failure (74). Renshaw (163) and Hunt (101, 102) distinguished between stimulating and paralyzing nicotinic actions of the onium compounds. Their criterion for a stimulating nicotinic action was a rise in blood pressure which was prevented by a large dose of nicotine. A compound was said to exhibit a paralyzing nicotinic action if it prevented the stimulating action of a small dose of nicotine.

Since these physiological actions are exhibited by the same compounds which give curariform paralysis, they must be taken into consideration when investigating compounds for possible therapeutic use. The presence of a stimulating nicotinic action would probably prevent the clinical use of a compound, although the paralyzing nicotinic action might not interfere and muscarinic action could be abolished by use of atropine. In the tabulation of compounds which possess curariform activity, the above physiological actions, when reported, have been indicated.

D. METHODS OF MEASUREMENT

The abolition of response of muscle to electrical stimulation of motor nerves has been used as a qualitative determination of curare activity (163). Several methods have been used in testing quantitatively for curare action. The most widely used has been the determination of the minimum dose necessary, when injected into the lymph sac, to cause complete paralysis in the frog. Other animals have been used to a lesser extent in complete paralysis experiments, but such a determination is more convenient with frogs.

The rabbit head-drop procedure (8, 31) is a rapid, accurate method for determining the intensity of curare paralysis. The solution of the compound to be tested is injected slowly into the ear vein of a rabbit and the dose adjusted so that the neck muscles fail to lift the chin in 2½ to 3 min. The end-point is very clear and reproducible. The dose required to produce the above effect can be reported in milligrams per kilogram of body weight, or the volume of test solution necessary to reach the end-point can be compared to a standard curare solution required to reach the same end-point in the same rabbit on the day preceding or following. In the second case the effectiveness of a compound is reported in units per milligram of the compound. A unit is defined as the activity of 1 milligram of the standard curare powder; hence the larger the value in units per milligram for a compound, the more effective it is.

Ing and coworkers (118–121) used isolated sartorius nerve–muscle preparations to determine the intensity of curare action. They measured the time for paralysis of the isolated nerve sartorius immersed in solutions of various compounds in concentrations of 0.1, 1, and 10 millimoles per liter.

IV. COMPOUNDS EXHIBITING CURARIFORM ACTIVITY

Although all onium ions, in general, exhibit curariform activity to some extent, a literature survey of only the most effective of these, the quaternary ammonium compounds, seemed worthwhile. The quaternary ammonium compounds (tables 1 to 19) have been organized into four large groups: alkylammonium compounds, arylalkylammonium compounds, heterocyclic ammonium compounds, and alkaloids. Each of these groups has been subdivided, with a table of related compounds for each subdivision. A definite order for listing compounds has been used in each table. The simplest and, in the case of the heterocyclic compounds, the most unsaturated derivatives appear first. That is, in the tetraalkylammonium derivatives the tetramethylammonium salt is listed first, followed by the compounds in which one methyl group is replaced by alkyl groups of increasing length, then by compounds in which two methyl groups have been replaced, etc. In the arylalkylammonium compounds the same general order is used with respect to the number of methyl groups on the nitrogen. In the heterocyclic compounds, the parent compound with simplest substituent is listed first, followed by increasing size and number of substituents, then by compounds of increasing saturation,—dihydro-, tetrahydro-, etc.

The alkaloids have been subdivided according to types, with various derivatives of each series listed in order of empirical formula or increasing substitution. The only alkaloids occurring naturally as the quaternary salts are the curare alkaloids. Although the erythrina alkaloids are effective as tertiary bases, the other types of alkaloids must be converted to quaternary derivatives before marked curariform activity is exhibited.

Table 20 contains the α-glycerol ethers, which have recently been proposed as possible curare substitutes.

In the discussion which follows each table the type of compound is taken up, with particular attention being given not only to the compounds which are most effective in their curariform activity but also to the effect of change of chemical structure or substituents on the various types of physiological action. Toxic doses of the various compounds have been recorded where possible in order to have this information readily available for consideration of margins of safety if any of the compounds are ever considered for drug use.

Explanation of symbols in the tables

The relative intensities of the types of actions are indicated by use of plus (+) signs. Three plus (+++) signs indicate a very pronounced action; two, a pronounced action; and one, a weak action. If the action is reported to be present and no notation is given as to the intensity, it is indicated by the symbol ⊕. A negative (−) sign indicates that the action was tested for and found to be absent. A question mark (?) indicates that the presence of the action is doubtful. In table 12 the letters d and p indicate depressor and pressor actions on the blood pressure.

The salt used in determining paralyzing or toxic doses is indicated in the same column with the dose. The letters and underlined numbers in the toxic dose columns indicate whether the lethal dose is the minimum lethal dose (M) or the dose required to kill a certain per cent of the animals ($\underline{50}$ = lethal dose for 50 per cent of the animals; $\underline{80}$ = LD 80, etc.). The absence of any of these symbols indicates that the dose was merely reported as the lethal dose. The method of injection is indicated by the following:

EL = endolymphal
IP = intraperitoneal
IV = intravenous
OS = oral
SC = subcutaneous

The rabbit head-drop method and tests with the isolated nerve sartorius were discussed on page 290.

A. ALKYLAMMONIUM COMPOUNDS

1. *Tetraalkylammonium compounds* (*table 1*)

In general, all of the tetraalkylammonium salts possess both curare and nicotinic action in varying degree. Muscarinic action may or may not be present.

Tetramethyl- and trimethylalkyl-ammonium salts have very pronounced curare actions, a maximum effectiveness in the trimethylalkyl series being reached with the butyl and amyl derivatives. The paralyzing power of these derivatives compares favorably with curare, as shown by comparison of the effectiveness of trimethylbutylammonium iodide on the isolated nerve preparation with that of curare (see table 14). Trimethyloctylammonium iodide was investigated clinically (19), but it caused vomiting. The muscarinic and stimu-

TABLE 1

Alkylammonium compounds

Tetraalkylammonium compounds

AMMONIUM COMPOUND	STRUCTURE	PHARMACOLOGICAL ACTION					TOXIC DOSES			PARALYZING DOSES			REFERENCES
		Curariform action	Muscarinic action	Stimulating nicotinic action	Paralyzing nicotinic action	Other actions	Frogs	Mice	Miscellaneous	Frogs	Minutes to paralyze isolated nerve sartorius, millimoles/liter 1	10	
							mg./kg.	*mg./kg.*	*mg./kg.*	*mg./kg.*	*minutes*		
Tetramethyl- .	$(CH_3)_4N^+$	++	++	++	++		Cl 10 EL	I 50 30 IP I 3 IV I 33–50 SC Cl 20 SC	Cats Cl 100 SC	Cl 5 EL	I 5.7		(5, 21, 32, 101, 102, 117, 120, 122, 146, 162, 211)
Trimethylethyl-	$(CH_3)_3N^+C_2H_5$	+	+	⊕				I 50 43 IP		Cl 10 EL	I 15	3.5	(5, 120, 146, 203, 211)
Trimethylpropyl-	$(CH_3)_3N^+C_3H_7$	+	⊕	+				I 50 68 IP			I 10		(5, 120, 162, 211)
Trimethylbutyl-.	$(CH_3)_3N^+C_4H_9$	++	+++	++	−			I 50 19 IP			I 2.5		(5, 101, 117, 120, 162, 211)
Trimethylamyl-	$(CH_3)_3N^+C_5H_{11}$	++	++	⊕			1 EL	I 50 18 IP	Cats 8–10 SC Rabbits 10–12 SC		I 5.5		(5, 32, 120, 162, 192, 193, 211)
Trimethyliso-amyl-.....	$(CH_3)_3N^+isoC_5H_{11}$	⊕	++				1 EL			Cl <10			(32, 193, 211)
Trimethylhexyl-.	$(CH_3)_3N^+C_6H_{13}$	++	++	++				I 50 24 IP			I 6		(5, 117, 120, 123, 162)
Trimethyl-heptyl-........	$(CH_3)_3N^+C_7H_{15}$	++	+	⊕				I 50 28 IP			I 6.5		(5, 120, 162, 211)
Trimethyloctyl-.	$(CH_3)_3N^+C_8H_{17}$	++	+	?	−			I 50 60 IP			I 6		(4, 5, 117, 120, 162, 211)

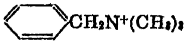
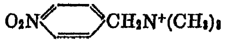
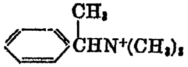
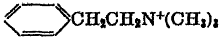
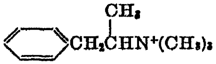
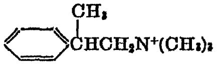
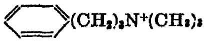
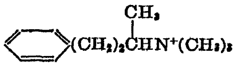
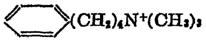
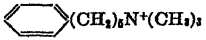
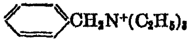
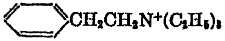
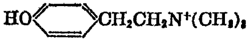
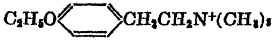
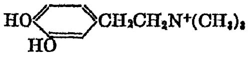
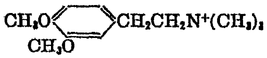
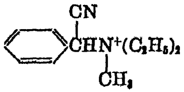
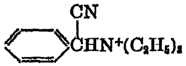
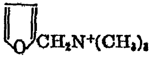
Trimethylnonyl-.	$(CH_3)_3N^+C_9H_{19}$		+	?	−			I $\underline{50}$ 46 IP					(4, 5)
Trimethylduodecyl-..........	$(CH_3)_3N^+C_{12}H_{25}$	+	⊕							Br 20	I 30		(24, 120)
Trimethylcetyl-..	$(CH_3)_3N^+C_{16}H_{33}$	⊕											(161)
Dimethyldiethyl-	$(CH_3)_2N^+(C_2H_5)_2$	+								Cl 13 EL	I	34	(120, 146, 162)
Methyltriethyl-...	$CH_3N^+(C_2H_5)_3$	+								Cl 20 EL	I	255	(117, 120, 146, 162)
Methyltributyl-..	$CH_3N^+(C_4H_9)_3$		−	⊕	−			30 SC					(101)
Tetraethyl-	$(C_2H_5)_4N^+$	+	−	−	⊕		Cl 25 EL	Cl 107-120 SC	Cats Cl >250 SC	Cl 20 EL	I	300	(21, 32, 101, 102, 111, 120, 123, 146, 162, 211)
Triethylpropyl-.	$(C_2H_5)_3N^+C_3H_7$	+											(136)
Triethylbutyl- ...	$(C_2H_5)_3N^+C_4H_9$	⊕	+	−	++			71 SC					(101, 136)
Triethylamyl-...	$(C_2H_5)_3N^+C_5H_{11}$	⊕											(136)
Triethyloctyl-....	$(C_2H_5)_3N^+C_8H_{17}$	⊕											(136)
Diethyldibutyl-.	$(C_2H_5)_2N^+(C_4H_9)_2$		−	−	++			17 SC					(101)
Ethyltributyl-.	$C_2H_5N^+(C_4H_9)_3$		−	−	++			24 SC					(101)
Tetrapropyl-....	$(C_3H_7)_4N^+$	⊕	−	−	++			52 SC		Cl 20-60	I 11.5		(32, 101, 117, 121, 162, 211)
Tripropylbutyl-.	$(C_3H_7)_3N^+C_4H_9$		−	⊕	++			25 SC					(101)
Tetrabutyl-	$(C_4H_9)_4N^+$	++	−	+	⊕			19 SC			I 6.5		(101, 117, 121, 162)
Tetraamyl-... .	$(C_5H_{11})_4N^+$	⊕											(211)
Benzyltrimethyl-		⊕	+++	++	++			I $\underline{50}$ 41.5 IP 35 SC		Br 40			(4, 24, 30, 101, 140, 161)
p-Nitrobenzyltrimethyl-.....										Br 100			(24)
α-Phenylethyltrimethyl-.......			⊕	⊕				I $\underline{50}$ 44 IP Br 55 SC					(4, 30, 111)

TABLE —*Co*

AMMONIUM COMPOUND	STRUCTURE	PHARMACOLOGICAL ACTION					TOXIC DOSES			PARALYZING DOSES			REFERENCES
		Curariform action	Muscarinic action	Stimulating nicotinic action	Paralyzing nicotinic action	Other actions	Frogs	Mice	Miscellaneous	Frogs	Minutes to paralyze isolated nerve sartorius, Millimoles/liter 1	10	
							mg./kg.	*mg./kg.*	*mg./kg.*	*mg./kg.*	*minutes*		
β-Phenylethyltrimethyl-.	 $CH_2CH_2N^+(CH_3)_3$	⊕	++	+++	–			I $\underline{50}$ 18.5 IP Br 80 SC		Br 15			(4, 24, 111, 140, 161)
(β-Phenyl-α-methylethyl)trimethyl-.... . ..	 $CH_2\overset{CH_3}{C}HN^+(CH_3)_3$		–	++				I $\underline{50}$ 31 IP					(4)
(β-Phenyl-β-methylethyl)-trimethyl-.....	 $\overset{CH_3}{C}HCH_2N^+(CH_3)_3$		–					I $\underline{50}$ 92 IP		I 30			(4, 24)
γ-Phenylpropyltrimethyl-. . .	 $(CH_2)_3N^+(CH_3)_3$		–	++	–			I $\underline{50}$ 10.5 IP					(4)
(γ-Phenyl-α-methylpropyl)-trimethyl-.. ...	 $(CH_2)_2\overset{CH_3}{C}HN^+(CH_3)_3$		–	++				I $\underline{50}$ 26 IP					(4)
4-Phenylbutyltrimethyl-	 $(CH_2)_4N^+(CH_3)_3$		–	⊕	–			I $\underline{50}$ 29 IP					(4)
5-Phenylamyltrimethyl-.........	 $(CH_2)_5N^+(CH_3)_3$		–	+	–			I $\underline{50}$ 33 IP					(4)

Benzyltriethyl-..			−	−	++			160 SC					(101)
β-Phenylethyltriethyl-.		⊕	−	−	⊕			I 80 SC			I 5.7		(111, 117, 120)
β-(p-Hydroxyphenyl)ethyltrimethyl-.......		⊕	−	+++	+++			I $\underline{50}$ 55 IP	I 5-10				(3, 6, 111, 140, 211)
β-(p-Ethoxyphenyl)ethyltrimethyl- ...			−	+									(140)
β-(3,4-Dihydroxyphenyl)ethyltrimethyl- .			−	+++	+++								(6, 111)
β-(3,4-Dimethoxyphenyl)ethyltrimethyl- ..			−	⊕									(140)
(Phenylcyanomethyl)methyldiethyl-... ...			−	−				I M 380 SC					(111)
(Phenylcyanomethyl)triethyl-			−	+	⊕			I M 200 SC					(111)
Furfuryltrimethyl-.. .			++	⊕	⊕			I $\underline{50}$ 10 SC					(37, 150)

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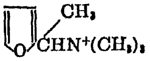
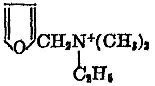
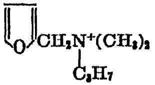
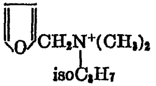
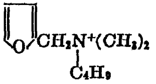
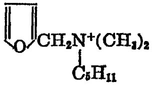
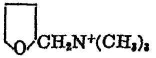
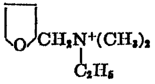
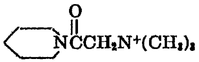
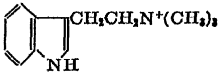
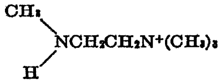
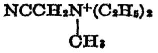
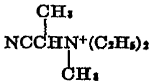
AMMONIUM COMPOUND	STRUCTURE	PHARMACOLOGICAL ACTION					TOXIC DOSES			PARALYZING DOSES			REFERENCES
		Curariform action	Muscarinic action	Stimulating nicotinic action	Paralyzing nicotinic action	Other actions	Frogs	Mice	Miscellaneous	Frogs	Minutes to paralyze isolated nerve sartorius, Millimoles/liter 1	Minutes to paralyze isolated nerve sartorius, Millimoles/liter 10	
							mg./kg.	*mg./kg.*	*mg./kg.*	*mg./kg.*	*minutes*		
α-Furylethyltrimethyl-…			⊕	+									(39)
Furfuryldimethylethyl-…			++	+	⊕			I $\underline{50}$ 400 SC					(37, 38, 39)
Furfuryldimethylpropyl-…			+										(37)
Furfuryldimethylisopropyl-…			+										(37)
Furfuryldimethylbutyl-			+										(37)
Furfuryldimethylamyl-…			+										(37)
Tetrahydrofurfuryltrimethy-…			⊕	⊕	⊕			I $\underline{50}$ 100 SC					(37, 38)

Tetrahydrofurfuryldimethylethyl-.........			⊕	⊕	⊕			I 50 700 SC					(37, 38)
Carbopiperidinomethyltrimethyl-... ..			⊕	–	–								(196a)
β-(3-Indole)ethyltrimethyl- .			⊕	++									(140, 196a)
Hydroxymethyltrimethyl- . .	$HOCH_2N^+(CH_3)_3$	(See formocholine, table 4)											
Iodomethyltrimethyl- .	$ICH_2N^+(CH_3)_3$		++	++				I M 80 SC					(102)
Nitromethyltrimethyl-..	$NO_2CH_2N^+(CH_3)_3$		+	+	–			Br M>1500 SC					(111)
β-Hydroxyethyltrimethyl-......	$HOCH_2CH_2N^+(CH_3)_3$	(See choline, table 4)											
β-Chloroethyltrimethyl-. . ..	$ClCH_2CH_2N^+(CH_3)_3$	⊕	⊕	⊕		Central depressant							(30, 153)
β-Bromoethyltrimethyl-	$BrCH_2CH_2N^+(CH_3)_3$	⊕	⊕	⊕				I M 250 SC					(30, 35, 116, 211)
β-Cyanoethyltrimethyl-	$NCCH_2CH_2N^+(CH_3)_3$	⊕	⊕										(30, 35)
β-Aminoethyltrimethyl-.. . ..	$H_2NCH_2CH_2N^+(CH_3)_3$	⊕	⊕			Central depressant							(30, 35, 153)
β-(Methylamino)-ethyltrimethyl-	 $(CH_3)(H)NCH_2CH_2N^+(CH_3)_3$	?	⊕			Central depressant							(153)
Cyanomethyldiethylmethyl-..	 $NCCH_2N^+(C_2H_5)_2(CH_3)$							I 250 SC					(99)
α-Cyanoethyldiethylmethyl-...	 $NCCH(CH_3)N^+(C_2H_5)_2(CH_3)$							I 400 SC					(99)

lating nicotinic actions shown by these compounds would probably prevent any therapeutic use.

The successive replacement of methyl groups with other alkyl groups reduces the muscarinic action to such an extent that tetraalkyl derivatives other than tetramethyl are devoid of muscarinic action. The replacement of methyl groups with ethyl groups reduces the intensity of curare action; however, the intensity again increases in the tetrapropyl- and tetrabutyl-ammonium compounds. The nicotinic action shows no general trends in these variations of the molecular structure.

Substitution of one alkyl group by an alkyl group containing a phenyl group, such as benzyl, β-phenylethyl, etc., in most cases eliminates the muscarinic action without affecting appreciably the other actions. However, triethylbenzyl- and triethyl-β-phenylethyl-ammonium salts possess neither muscarinic nor stimulating nicotinic actions, and the latter possesses a very pronounced curare action on the isolated nerve sartorius. Alles (4) showed that the introduction of a methyl group in the phenylalkyl chain in the position α to the nitrogen greatly decreases both muscarinic and nicotinic actions.

Furfuryltrialkylammonium salts possess both muscarinic and nicotinic actions, but no information is available on their curare action. Fellows and Livingston (37) reported that saturation of the furan ring decreases the physiological potency with little effect on the toxicity.

2. Neurine derivatives and analogues (table 2)

Neurine acts in accord with the rule concerning the relation between the physiological actions of compounds containing saturated and unsaturated groups (32), which states that the unsaturated compounds are more toxic and generally more effective physiologically than the corresponding saturated compounds. Neurine is more toxic and has more pronounced muscarinic and nicotinic actions than ethyltrimethylammonium salts. Hunt and Renshaw (102) reported that neurine also possesses a depressant action on autonomic ganglia. In general, all derivatives and analogues of neurine possess curare actions, but they also have marked muscarinic and nicotinic actions. Of this series, only ethynyltrimethylammonium salts are reported to possess a very pronounced curare action (191).

3. Muscarine derivatives and analogues (table 3)

Muscarine is the drug responsible for the poisonous effects of certain species of mushrooms. It has no curare or nicotinic action. It has such a definite action that the term "muscarinic" is used to designate the particular response of heart, smooth muscle, and glands to its stimulation. The criterion for muscarinic action was discussed on page 289. The analogues of muscarine have never been found to possess any marked curare activity (68, 74).

4. Choline derivatives and analogues (table 4)

Choline possesses the three pharmacological actions of quaternary ammonium bases,—muscarinic, nicotinic, and curariform. Derivatives of choline may

TABLE

Alkylammonium compounds

Neurine derivatives and analogues

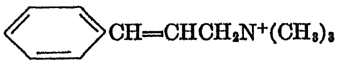
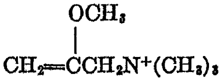
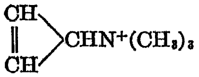
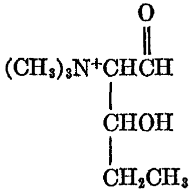
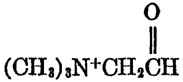
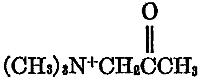
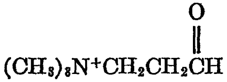
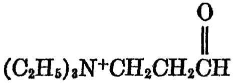
AMMONIUM COMPOUND	STRUCTURE	PHARMACOLOGICAL ACTION					TOXIC DOSES			PARALYZING DOSES	REFERENCES
		Curariform action	Muscarinic action	Stimulating nicotinic action	Paralyzing nicotinic action	Other actions	Frogs	Mice	Miscellaneous	Frogs	
							mg./kg.	*mg./kg.*	*mg./kg.*		
Vinyltrimethyl-... (Neurine)	$CH_2{=}CHN^+(CH_3)_3$	⊕	++	++	⊕		1–2 SC	Br M 73 SC OH M 46 SC 2.5 IP	Rabbits 40–50 SC		(101, 102, 107, 211)
Allyltrimethyl-.... (Homoneurine)	$CH_2{=}CHCH_2N^+(CH_3)_3$		++	++	⊕			Cl M 200 SC I M 250 SC OH M 130 SC			(101, 107, 116)
Isocrotyltri-methyl-.........	$CH_3CH{=}CHCH_2N^+(CH_3)_3$									>20 mg.	(211)
γ-Phenylallyltri-methyl-.........			−	+++				I 50 21 IP			(4)
β-Methoxyallyl-trimethyl-	 $CH_2{=}C(OCH_3)CH_2N^+(CH_3)_3$	−	++	−	−	Ca-thar-tic			Cats Br 1–5		(85)
Trimethinetri-methyl-.........		+									(211)
Ethynyltrimethyl-	$HC{\equiv}CN^+(CH_3)_3$	++					M 30 EL			1 mg.	(32, 191, 211)

TABLE 3

Alkylammonium compounds

Muscarine derivatives and analogues

AMMONIUM COMPOUND	STRUCTURE	PHARMACOLOGICAL ACTION				TOXIC DOSE	PARALYZING DOSE	REFERENCES
		Curari-form action	Musca-rinic action	Stimu-lating nico-tinic action	Para-lyzing nico-tinic action	Frogs	Frogs	
						mg./kg.	*mg./kg.*	
(α-Formyl-β-hydroxybutyl)trimethyl- (Muscarine)	 $(CH_3)_3N^+\underset{\substack{\vert\\ CHOH\\ \vert\\ CH_2CH_3}}{CH}\overset{\substack{O\\ \Vert}}{C}H$	–	+++	–	–	1 EL		(2, 30, 32)
Formylmethyltrimethyl-	 $(CH_3)_3N^+CH_2\overset{\substack{O\\ \Vert}}{C}H$		⊕					(14, 66)
Acetonyltrimethyl	 $(CH_3)_3N^+CH_2\overset{\substack{O\\ \Vert}}{C}CH_3$		–				Cl 300	(14, 24)
β-Formylethyltrimethyl-	 $(CH_3)_3N^+CH_2CH_2\overset{\substack{O\\ \Vert}}{C}H$		⊕					(14)
β-Formylethyltriethyl-	 $(C_2H_5)_3N^+CH_2CH_2\overset{\substack{O\\ \Vert}}{C}H$		⊕					(14)

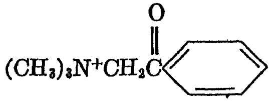
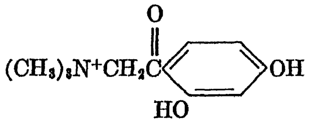
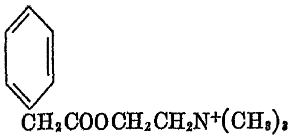
Benzoylmethyltrimethyl-							50	(24)
2,4-Dihydroxybenzoylmethyltrimethyl-				⊕	⊕		Cl 30	(6,24)

TABLE 4

Alkylammonium compounds

Choline derivatives and analogues

CHOLINE DERIVATIVE	STRUCTURE OF CATION	PHARMACOLOGICAL ACTION						TOXIC DOSES		PARALYZING DOSE	REFERENCES
		Curariform action	Muscarinic action	Nicotinic action	Stimulating nicotinic action	Paralyzing nicotinic action	Atropine action	Mice	Miscellaneous		
								mg./kg.	*mg./kg.*	*mg./kg.*	
Choline.......... . .	$HOCH_2CH_2N^+(CH_3)_3$	+	⊕	⊕	⊕			Cl M 740–50 SC	Cats M 250 IV	Mice 500	(32, 74, 102, 115, 116, 117)
Formylcholine.......	$HCOOCH_2CH_2N^+(CH_3)_3$	⊕	++								(30, 35)
Acetylcholine........	$CH_3COOCH_2CH_2N^+(CH_3)_3$	⊕	+++	⊕	−			Cl M 310 SC Br M 300 SC Cl $\underline{50}$ 20 IV Cl $\underline{50}$ 170 SC Cl 5000 OS	Rats 22 IV 250 SC 2500 OS		(35, 74, 102, 108, 115, 135, 149)
Acetyl-*d*₃-choline	$Cd_3COOCH_2CH_2N^+(CH_3)_3$		++		⊕						(34, 115)
Chloroacetylcholine..	$ClCH_2COOCH_2CH_2N^+(CH_3)_3$		⊕	++				Br M 700 SC			(30, 102)
Propionylcholine......	$C_2H_5COOCH_2CH_2N^+(CH_3)_3$		++	⊕							(194)
Butyrylcholine..... .	$C_3H_7COOCH_2CH_2N^+(CH_3)_3$		+	++							(115, 194)
Isobutyrylcholine....	iso-$C_3H_7COOCH_2CH_2N^+(CH_3)_3$		+	+							(115)
Valerylcholine.......	$C_4H_9COOCH_2CH_2N^+(CH_3)_3$		+	⊕							(115)
Lactylcholine........	$CH_3CHOHCOOCH_2CH_2N^+(CH_3)_3$	⊕	++								(30, 35)
Phenylacetylcholine...	 $C_6H_5CH_2COOCH_2CH_2N^+(CH_3)_3$		+	++				Cl M >500 SC			(87, 115)

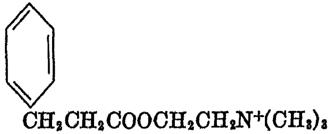
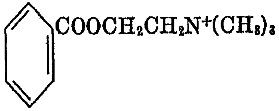
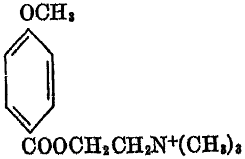
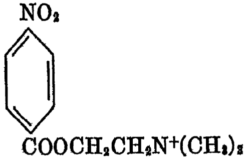
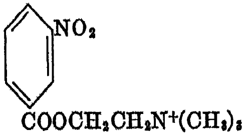
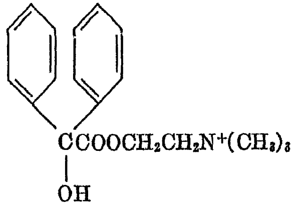
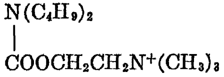
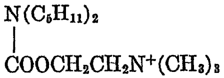
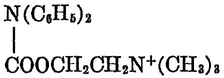
Phenylpropionylcholine	 $C_6H_5CH_2CH_2COOCH_2CH_2N^+(CH_3)_3$		⊕	++						(115)
Succinoylcholine	$CH_2COOCH_2CH_2N^+(CH_3)_3$ $\vert$ $CH_2COOCH_2CH_2N^+(CH_3)_3$		+		⊕					(115)
Benzoylcholine	 $C_6H_5COOCH_2CH_2N^+(CH_3)_3$		+		++			Cl M 2000 SC		(115, 116)
Anisoylcholine	 OCH_3; $COOCH_2CH_2N^+(CH_3)_3$				⊕					(115)
p-Nitrobenzoylcholine	 NO_2; $COOCH_2CH_2N^+(CH_3)_3$		+							(115)
m-Nitrobenzoylcholine	 NO_2; $COOCH_2CH_2N^+(CH_3)_3$		++							(115)

TABLE 4—*Continued*

CHOLINE DERIVATIVE	STRUCTURE OF CATION	PHARMACOLOGICAL ACTION						TOXIC DOSES		PARALYZING DOSE	REFERENCES
		Curariform action	Muscarinic action	Nicotinic action	Stimulating nicotinic action	Paralyzing nicotinic action	Atropine action	Mice	Miscellaneous		
								mg./kg.	*mg./kg.*	*mg./kg.*	
Benzilylcholine.......							⊕				(119)
Carbamylcholine.. ... (Carbaminoylcholine)	$H_2NCOOCH_2CH_2N^+(CH_3)_3$		++	++	++			Cl 0.5 IV Cl 1.5 SC Cl $\underline{50}$ 0.3 IV Cl $\underline{50}$ 3 OS	Rats 4 SC 0.1 IV 40 OS		(2, 37, 38, 74, 135, 149)
Dibutylcarbamylcholine..	 $\begin{array}{l} N(C_4H_9)_2 \\ \vert \\ COOCH_2CH_2N^+(CH_3)_3 \end{array}$		–		–		⊕				(203)
Diamylcarbamylcholine...............	 $\begin{array}{l} N(C_5H_{11})_2 \\ \vert \\ COOCH_2CH_2N^+(CH_3)_3 \end{array}$						⊕				(203)
Diphenylcarbamylcholine	 $\begin{array}{l} N(C_6H_5)_2 \\ \vert \\ COOCH_2CH_2N^+(CH_3)_3 \end{array}$						⊕				(203)

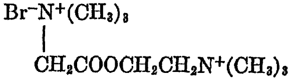
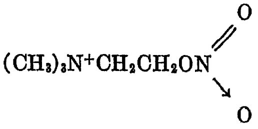
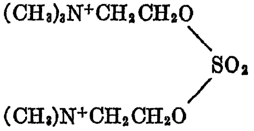
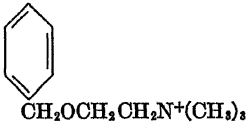
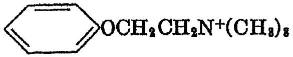
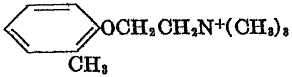
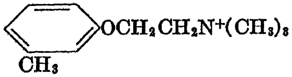
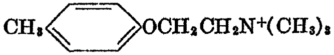
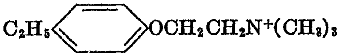
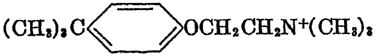
Glycylcholine.........	$H_2NCH_2COOCH_2CH_2N^+(CH_3)_3$	–	–		–	–	–				(224)
N-Trimethylglycylcholine bromide.....	 $Br^-N^+(CH_3)_3$ — $CH_2COOCH_2CH_2N^+(CH_3)_3$	–	+		–	–	–				(224)
Choline nitrite........	$(CH_3)_3N^+CH_2CH_2ON{=}O$	⊕	++	⊕							(2, 30, 35, 128)
Choline nitrate.......		⊕	++	++	⊕			M 210 SC	Frogs 20 EL	Frogs 2 EL	(30, 32, 35, 102)
Choline sulfate......			–	–	–			M 1000 SC			(105)
Choline dimethylphosphate..	$(CH_3)_3N^+CH_2CH_2OPO(OCH_3)_2$		+		+++			Cl M 44 SC			(105, 174)
Choline methyl ether.	$CH_3OCH_2CH_2N^+(CH_3)_3$	⊕	++	⊕							(35, 194)
Choline ethyl ether..	$C_2H_5OCH_2CH_2N^+(CH_3)_3$	⊕	++	⊕							(35, 194)
Choline propyl ether..	$C_3H_7OCH_2CH_2N^+(CH_3)_3$	⊕	++								(30, 35)
Choline butyl ether..	$C_4H_9OCH_2CH_2N^+(CH_3)_3$		+		++						(194)
Choline hydroxyethyl ether..	$HOCH_2CH_2OCH_2CH_2N^+(CH_3)_3$									Frogs Cl 30	(24)

TABLE 4—*Continued*

CHOLINE DERIVATIVE	STRUCTURE OF CATION	PHARMACOLOGICAL ACTION						TOXIC DOSES		PARALYZING DOSE	REFERENCES
		Curariform action	Muscarinic action	Nicotinic action	Stimulating nicotinic action	Paralyzing nicotinic action	Atropine action	Mice	Miscellaneous		
								mg./kg.	*mg./kg.*	*mg./kg.*	
Choline vinyl ether...	$CH_2{=}CHOCH_2CH_2N^+(CH_3)_3$		++		++						(194)
Choline benzyl ether..			–		–			Br M 38 SC			(114)
Choline phenyl ether..			–	+++				Cl M 85 SC			(105, 114)
Choline *o*-tolyl ether..			–		++	++		Br M 20 SC			(114)
Choline *m*-tolyl ether..			–		⊕			Br M 42 SC			(114)
Choline *p*-tolyl ether.			–		⊕			Br M 29 SC			(114)
Choline *p*-ethylphenyl ether..............			–		⊕			Br M 85 SC			(114)
Choline *p-tert*-butylphenyl ether........			–		–			Br M 500 SC			(114)

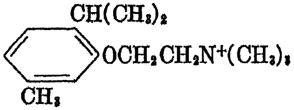
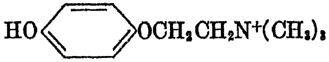
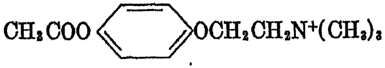
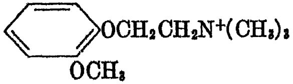
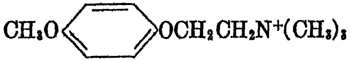
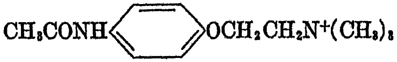
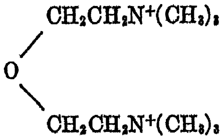
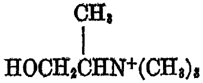
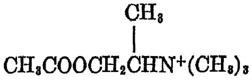
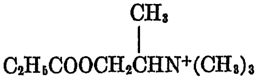
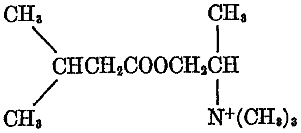
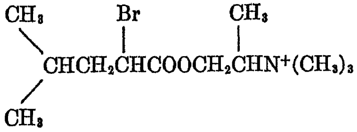
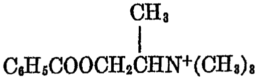
Choline 2-isopropyl-5-methylphenyl ether.			–		+			Br M 500 SC			(114)
Choline p-hydroxyphenyl ether........			–		⊕			Br M 230 SC			(107)
Choline p-acetoxyphenyl ether........			–		⊕			Br M >1400 SC			(107)
Choline o-methoxyphenyl ether........			–		⊕			Br M 100 SC			(107)
Choline p-methoxyphenyl ether........			–		⊕			Br M 600 SC			(107)
Choline p-acetaminophenyl ether........			–		–			Br M 170 SC			(107)
β-Ethoxycholine ethyl ether..............	$(C_2H_5O)_2CHCH_2N^+(CH_3)_3$		–								(14)
Dicholine ether.......	 CH$_2$CH$_2$N$^+$(CH$_3$)$_3$ O CH$_2$CH$_2$N$^+$(CH$_3$)$_3$	⊕	⊕								(30, 35)
α-Methylcholine......	 $HOCH_2\overset{CH_3}{\overset{\vert}{C}}HN^+(CH_3)_3$							Cl M 1000 SC			(100)

TABLE 4—*Continued*

CHOLINE DERIVATIVE	STRUCTURE OF CATION	PHARMACOLOGICAL ACTION						TOXIC DOSES		PARALYZING DOSE	REFERENCES
		Curariform action	Muscarinic action	Nicotinic action	Stimulating nicotinic action	Paralyzing nicotinic action	Atropine action	Mice	Miscellaneous		
								mg./kg.	*mg./kg.*	*mg./kg.*	
Acetyl-α-methylcholine....	 $CH_3COOCH_2\overset{\overset{CH_3}{\vert}}{C}HN^+(CH_3)_3$	—	⊕		⊕			Cl M 350 SC			(75, 100, 125)
Propionyl-α-methylcholine....	 $C_2H_5COOCH_2\overset{\overset{CH_3}{\vert}}{C}HN^+(CH_3)_3$							Cl M 1600 SC			(100)
Isovaleryl-α-methylcholine....								Cl M 1600 SC			(100)
α-Bromoisocapryl-α-methylcholine....								Cl M 1000 SC			(100)
Benzoyl-α-methylcholine....	 $C_6H_5COOCH_2\overset{\overset{CH_3}{\vert}}{C}HN^+(CH_3)_3$							Cl M 900 SC			(100)

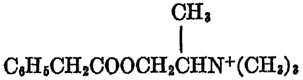
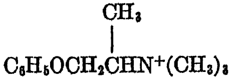
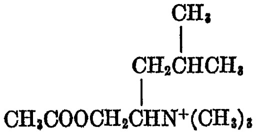
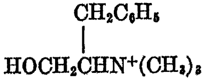
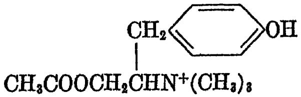
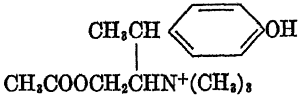
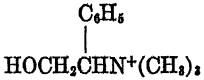
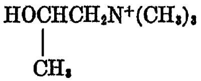
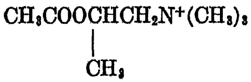
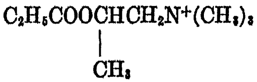
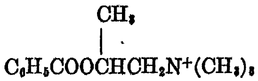
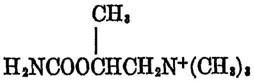
Phenylacetyl-α-methyl-choline............	 $C_6H_5CH_2COOCH_2\overset{\overset{CH_3}{\vert}}{C}HN^+(CH_3)_3$							Cl M >2000 SC			(100)
α-Methylcholine phenyl ether........	 $C_6H_5OCH_2\overset{\overset{CH_3}{\vert}}{C}HN^+(CH_3)_3$				⊕						(114)
Acetyl-α-isobutylcholine................	 $CH_3COOCH_2\overset{\overset{\overset{\overset{CH_3}{\vert}}{CH_2CHCH_3}}{\vert}}{C}HN^+(CH_3)_3$		⊕		⊕						(75, 125)
α-Benzylcholine.......	 $HOCH_2\overset{\overset{CH_2C_6H_5}{\vert}}{C}HN^+(CH_3)_3$	+	⊕	⊕							(141)
Acetyl-α-(p-hydroxy-benzyl)choline.....			⊕		⊕						(75, 125)
Acetyl-α-(α-p-hydroxy-phenylethyl)choline........			⊕		⊕						(75, 125)
α-Phenylcholine......	 $HOCH_2\overset{\overset{C_6H_5}{\vert}}{C}HN^+(CH_3)_3$	+	⊕	⊕							(141)

TABLE 4—*Continued*

CHOLINE DERIVATIVE	STRUCTURE OF CATION	PHARMACOLOGICAL ACTION						TOXIC DOSES		PARALYZING DOSE	REFERENCES
		Curariform action	Muscarinic action	Nicotinic action	Stimulating nicotinic action	Paralyzing nicotinic action	Atropine action	Mice	Miscellaneous		
								mg./kg.	*mg./kg.*	*mg./kg.*	
β-Methylcholine.......	 $\underset{\displaystyle CH_3}{HOCH}CH_2N^+(CH_3)_3$		⊕		⊕			Cl M 630 SC	Cats 75 SC 20 IV 750 OS		(74, 113, 116)
Acetyl-β-methylcholine.................	 $CH_3COO\underset{\displaystyle CH_3}{CH}CH_2N^+(CH_3)_3$		+++	−	+	+		Cl M 175 SC Cl $\underline{50}$ 90 SC Cl $\underline{50}$ 20 IV			(2, 38, 74, 113, 116, 141)
Propionyl-β-methylcholine............	 $C_2H_5COO\underset{\displaystyle CH_3}{CH}CH_2N^+(CH_3)_3$		++	−							(113, 194)
Benzoyl-β-methylcholine................	 $C_6H_5COO\overset{\displaystyle CH_3}{CH}CH_2N^+(CH_3)_3$							Cl M 1080 SC			(116)
Carbamyl-β-methylcholine	 $H_2NCOO\overset{\displaystyle CH_3}{CH}CH_2N^+(CH_3)_3$			−			⊕	Cl $\underline{50}$ 120 SC Cl $\underline{50}$ 10 IV			(149, 203)

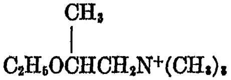
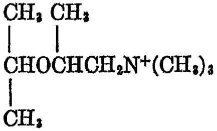
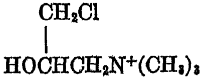
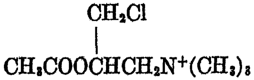
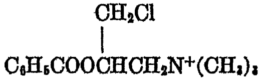
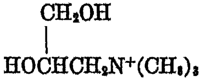
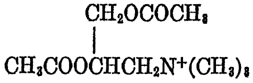
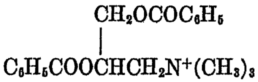
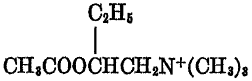
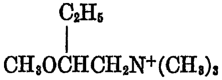
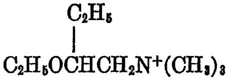
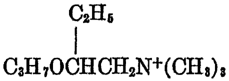
β-Methylcholine methyl ether........	$CH_3O\overset{\overset{CH_3}{\mid}}{C}HCH_2N^+(CH_3)_3$	⊕	++	+				I M 110 SC			(114, 195)
β-Methylcholine ethyl ether....	 $C_2H_5O\overset{\overset{CH_3}{\mid}}{C}HCH_2N^+(CH_3)_3$		++	−	−			Cl 50 250 SC Cl 50 30 IV I M 140 SC			(2, 114, 140, 149, 194)
β-Methylcholine iso-propyl ether........	 $\underset{\underset{CH_3}{\mid}}{\overset{\overset{CH_3}{\mid}}{C}}HO\overset{\overset{CH_3}{\mid}}{C}HCH_2N^+(CH_3)_3$		⊕		+			I M 220 SC			(114)
β-Methylcholine butyl ether..............	$C_4H_9O\overset{\overset{CH_3}{\mid}}{C}HCH_2N^+(CH_3)_3$	⊕	+	+							(195)
β-Chloromethylcholine.................	 $HO\overset{\overset{CH_2Cl}{\mid}}{C}HCH_2N^+(CH_3)_3$							Cl M 500 SC			(116)
Acetyl-β-chloromethylcholine............	 $CH_3COO\overset{\overset{CH_2Cl}{\mid}}{C}HCH_2N^+(CH_3)_3$							Cl M 365 SC			(116)
Benzoyl-β-chloro-methylcholine..	 $C_6H_5COO\overset{\overset{CH_2Cl}{\mid}}{C}HCH_2N^+(CH_3)_3$							Cl M 356 SC			(116)
β-Hydroxymethylcholine.............. ..	 $HO\overset{\overset{CH_2OH}{\mid}}{C}HCH_2N^+(CH_3)_3$							Cl M 1800 SC			(116)

TABLE 4—*Continued*

CHOLINE DERIVATIVE	STRUCTURE OF CATION	PHARMACOLOGICAL ACTION						TOXIC DOSES		PARALYZING DOSE	REFERENCES
		Curariform action	Muscarinic action	Nicotinic action	Stimulating nicotinic action	Paralyzing nicotinic action	Atropine action	Mice	Miscellaneous		
								mg./kg.	*mg./kg.*	*mg./kg.*	
Acetyl-β-acetoxy-methylcholine.......	 $CH_3COO\overset{\overset{CH_2OCOCH_3}{\vert}}{C}HCH_2N^+(CH_3)_3$							Cl M 1000 SC			(116)
Benzoyl-β-benzoyloxy-methylcholine......	 $C_6H_5COO\overset{\overset{CH_2OCOC_6H_5}{\vert}}{C}HCH_2N^+(CH_3)_3$							Cl M 1200 SC			(116)
Acetyl-β-ethylcholine..	 $CH_3COO\overset{\overset{C_2H_5}{\vert}}{C}HCH_2N^+(CH_3)_3$		++	+							(195)
β-Ethylcholine methyl ether..............	 $CH_3O\overset{\overset{C_2H_5}{\vert}}{C}HCH_2N^+(CH_3)_3$		⊕	−							(195)
β-Ethylcholine ethyl ether.............	 $C_2H_5O\overset{\overset{C_2H_5}{\vert}}{C}HCH_2N^+(CH_3)_3$		⊕	−							(195)
β-Ethylcholine propyl ether..............	 $C_3H_7O\overset{\overset{C_2H_5}{\vert}}{C}HCH_2N^+(CH_3)_3$	++	−	−							(195)

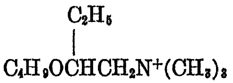
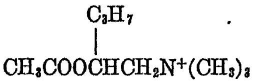
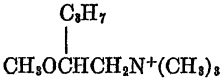
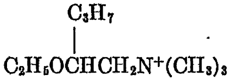
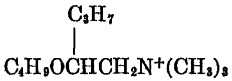
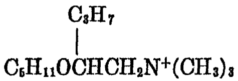
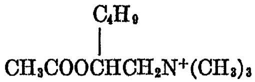
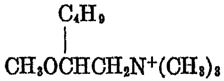
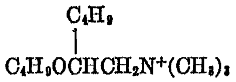
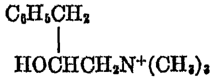
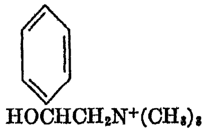
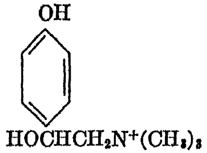
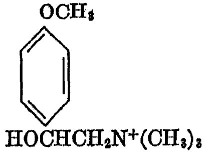
β-Ethylcholine butyl ether	 $C_4H_9O\overset{C_2H_5}{\overset{\vert}{C}}HCH_2N^+(CH_3)_3$	++	−	−							(195)
Acetyl-β-propylcholine	 $CH_3COO\overset{C_3H_7}{\overset{\vert}{C}}HCH_2N^+(CH_3)_3$		⊕								(196)
β-Propylcholine methyl ether	 $CH_3O\overset{C_3H_7}{\overset{\vert}{C}}HCH_2N^+(CH_3)_3$		+	−							(195)
β-Propylcholine ethyl ether	 $C_2H_5O\overset{C_3H_7}{\overset{\vert}{C}}HCH_2N^+(CH_3)_3$		⊕	−							(195)
β-Propylcholine butyl ether	 $C_4H_9O\overset{C_3H_7}{\overset{\vert}{C}}HCH_2N^+(CH_3)_3$	++	−	−							(195)
β-Propylcholine amyl ether	 $C_5H_{11}O\overset{C_3H_7}{\overset{\vert}{C}}HCH_2N^+(CH_3)_3$	++	−	−							(195)
Acetyl-β-butylcholine	 $CH_3COO\overset{C_4H_9}{\overset{\vert}{C}}HCH_2N^+(CH_3)_3$		⊕								(196)
β-Butylcholine methyl ether	 $CH_3O\overset{C_4H_9}{\overset{\vert}{C}}HCH_2N^+(CH_3)_3$		⊕	⊕							(195)
β-Butylcholine ethyl ether	$C_2H_5O\overset{C_4H_9}{\overset{\vert}{C}}HCH_2N^+(CH_3)_3$		−	−							(195)

TABLE 4—*Continued*

CHOLINE DERIVATIVE	STRUCTURE OF CATION	PHARMACOLOGICAL ACTION						TOXIC DOSES		PARALYZING DOSE	REFERENCES
		Curariform action	Muscarinic action	Nicotinic action	Stimulating nicotinic action	Paralyzing nicotinic action	Atropine action	Mice	Miscellaneous		
								mg./kg.	*mg./kg.*	*mg./kg.*	
β-Butylcholine butyl ether	 $\overset{C_4H_9}{\overset{\vert}{C_4H_9OCHCH_2N^+(CH_3)_3}}$	⊕	–	–							(196)
β-Benzylcholine	 $\underset{HOCHCH_2N^+(CH_3)_3}{\underset{\vert}{C_6H_5CH_2}}$	⊕	–	–							(196)
β-Phenylcholine			⊕		⊕						(140)
β-(*p*-Hydroxyphenyl)-choline			⊕		+						(140)
β-(*p*-Methoxyphenyl)-choline			⊕		⊕						(136, 140)

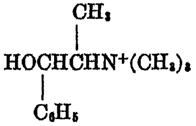
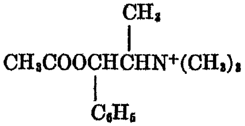
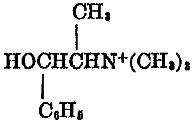
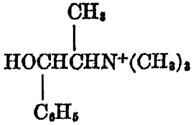
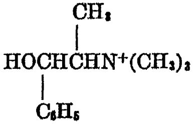
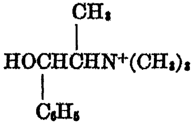
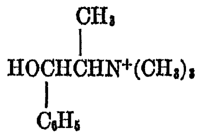
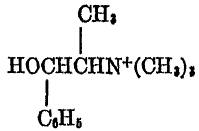
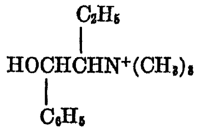
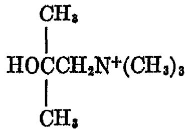
N-Methylephedrine methohydroxide ...	 $\underset{C_6H_5}{\underset{\vert}{HOCH}}\overset{CH_3}{\overset{\vert}{CH}}N^+(CH_3)_3$	–								Frogs I 30 Rabbits 15	(24, 117)
Acetyl-*N*-methylephedrine methohydroxide	 $CH_3COO\underset{C_6H_5}{\underset{\vert}{CH}}\overset{CH_3}{\overset{\vert}{CH}}N^+(CH_3)_3$		–		–			M 270 SC			(114)
d-*N*-Methylephedrine methohydroxide.....	 $\underset{C_6H_5}{\underset{\vert}{HOCH}}\overset{CH_3}{\overset{\vert}{CH}}N^+(CH_3)_3$		–		⊕						(140)
l-*N*-Methylephedrine methohydroxide.....	 $\underset{C_6H_5}{\underset{\vert}{HOCH}}\overset{CH_3}{\overset{\vert}{CH}}N^+(CH_3)_3$		–		+						(140)
dl-*N*-Methylephedrine methohydroxide.....	 $\underset{C_6H_5}{\underset{\vert}{HOCH}}\overset{CH_3}{\overset{\vert}{CH}}N^+(CH_3)_3$		–		+						(140)
d-*N*-Methyl-ψ-ephedrine methohydroxide	 $\underset{C_6H_5}{\underset{\vert}{HOCH}}\overset{CH_3}{\overset{\vert}{CH}}N^+(CH_3)_3$		–		⊕						(140)

TABLE 4—*Continued*

CHOLINE DERIVATIVE	STRUCTURE OF CATION	PHARMACOLOGICAL ACTION						TOXIC DOSES		PARALYZING DOSE	REFERENCES
		Curariform action	Muscarinic action	Nicotinic action	Stimulating nicotinic action	Paralyzing nicotinic action	Atropine action	Mice	Miscellaneous		
								mg./kg.	*mg./kg.*	*mg./kg.*	
l-*N*-Methyl-ψ-ephedrine methohydroxide	 $\mathrm{HO}\underset{\underset{\mathrm{C_6H_5}}{\vert}}{\mathrm{C}}\mathrm{H}\overset{\overset{\mathrm{CH_3}}{\vert}}{\mathrm{C}}\mathrm{HN^+(CH_3)_3}$		–		⊕						(140)
dl-*N*-Methyl-ψ-ephedrine methohydroxide	 $\mathrm{HO}\underset{\underset{\mathrm{C_6H_5}}{\vert}}{\mathrm{C}}\mathrm{H}\overset{\overset{\mathrm{CH_3}}{\vert}}{\mathrm{C}}\mathrm{HN^+(CH_3)_3}$		–		⊕						(140)
α-Ethyl-β-phenylcholine	 $\mathrm{HO}\underset{\underset{\mathrm{C_6H_5}}{\vert}}{\mathrm{C}}\mathrm{H}\overset{\overset{\mathrm{C_2H_5}}{\vert}}{\mathrm{C}}\mathrm{HN^+(CH_3)_3}$		⊕		⊕						(140)
β,β-Dimethylcholine	 $\mathrm{HO}\overset{\overset{\mathrm{CH_3}}{\vert}}{\underset{\underset{\mathrm{CH_3}}{\vert}}{\mathrm{C}}}\mathrm{CH_2N^+(CH_3)_3}$		⊕		⊕			Cl M 700 SC			(116, 140)

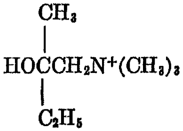
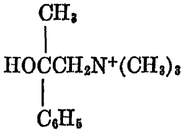
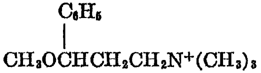
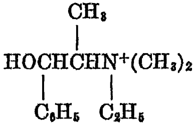
β-Methyl-β-ethyl-choline	 $HO\overset{CH_3}{\underset{C_2H_5}{C}}CH_2N^+(CH_3)_3$							Cl M 610 SC			(116)
β-Methyl-β-phenyl-choline	 $HO\overset{CH_3}{\underset{C_6H_5}{C}}CH_2N^+(CH_3)_3$				⊕			Cl M 450 SC			(116, 136)
Formocholine	$HOCH_2N^+(CH_3)_3$							Cl M 70–75 SC			(107, 116)
Acetylformocholine	$CH_3COOCH_2N^+(CH_3)_3$		++		⊕			Cl M > 170 SC			(102)
Formocholine methyl ether	$CH_3OCH_2N^+(CH_3)_3$	⊕	⊕		⊕			Cl M 37 SC Cl M 40 SC			(35, 107, 110, 116)
Formocholine ethyl ether	$C_2H_5OCH_2N^+(CH_3)_3$	⊕									(35)
Formocholine propyl ether	$C_3H_7OCH_2N^+(CH_3)_3$	⊕	++		⊕						(35, 110)
Formocholine allyl ether	$CH_2{=}CHCH_2OCH_2N^+(CH_3)_3$		⊕		⊕			I M 52 SC			(107)
Formocholine butyl ether	$C_4H_9OCH_2N^+(CH_3)_3$	⊕	⊕		⊕			I M 71 SC			(35, 107)
Formocholine isobutyl ether	iso-$C_4H_9OCH_2N^+(CH_3)_3$		⊕		⊕			I M 54 SC I M 52 SC			(107, 110)

TABLE 4—*Continued*

CHOLINE DERIVATIVE	STRUCTURE OF CATION	PHARMACOLOGICAL ACTION						TOXIC DOSES		PARALYZING DOSE	REFERENCES
		Curariform action	Muscarinic action	Nicotinic action	Stimulating nicotinic action	Paralyzing nicotinic action	Atropine action	Mice	Miscellaneous		
								mg./kg.	*mg./kg.*	*mg./kg.*	
γ-Homocholine	$HO(CH_2)_3N^+(CH_3)_3$		++	+				Cl M 170 SC			(116, 153)
Acetyl-γ-homocholine	$CH_3COO(CH_2)_3N^+(CH_3)_3$							Cl M 70 SC			(116)
Benzoyl-γ-homocholine	$C_6H_5COO(CH_2)_3N^+(CH_3)_3$							Cl M 270 SC			(116)
γ-Homocholine methyl ether	$CH_3OCH_2CH_2CH_2N^+(CH_3)_3$	⊕	⊕		⊕	⊕					(193b)
γ-Homocholine allyl ether	$CH_2{=}CHCH_2O(CH_2)_3N^+(CH_3)_3$		–								(211)
γ-Homocholine phenyl ether	$C_6H_5OCH_2CH_2CH_2N^+(CH_3)_3$		–	⊕	+			Cl M 180 SC			(105)
γ-Phenylhomocholine methyl ether	 $CH_3OCH(C_6H_5)CH_2CH_2N^+(CH_3)_3$	⊕	–	++							(193a)
Ammonium compounds related to choline											
(α-Methyl-β-phenyl-β-hydroxyethyl)dimethylethyl	 $HOCH(C_6H_5)CH(CH_3)N^+(CH_3)_2(C_2H_5)$		⊕		⊕						(140)

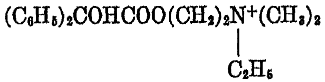
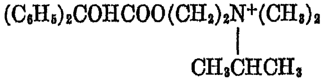
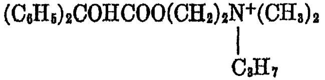
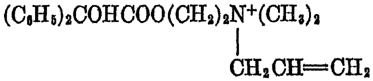
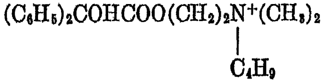
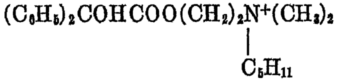
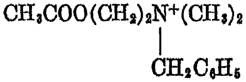
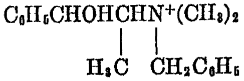
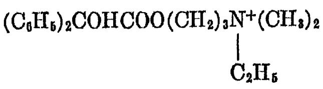
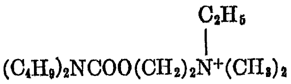
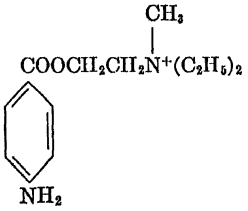
β-Benzilyloxyethyl-dimethylethyl.......	 $(C_6H_5)_2COHCOO(CH_2)_2\underset{C_2H_5}{N^+}(CH_3)_2$						⊕	Cl Cl Cl	$\underline{50}$ $\underline{50}$ $\underline{50}$	40 160 1000	IP SC OS			(119)
β-Benzilyloxyethyl-dimethylisopropyl...	 $(C_6H_5)_2COHCOO(CH_2)_2\underset{CH_3CHCH_3}{N^+}(CH_3)_2$						⊕	Cl Cl	$\underline{50}$ $\underline{50}$	40 75	IP SC			(119)
β-Benzilyloxyethyl-dimethylpropyl......	 $(C_6H_5)_2COHCOO(CH_2)_2\underset{C_3H_7}{N^+}(CH_3)_2$						⊕							(119)
β-Benzilyloxyethyl-dimethylallyl...	 $(C_6H_5)_2COHCOO(CH_2)_2\underset{CH_2CH{=}CH_2}{N^+}(CH_3)_2$						⊕							(119)
β-Benzilyloxyethyl-dimethylbutyl	 $(C_6H_5)_2COHCOO(CH_2)_2\underset{C_4H_9}{N^+}(CH_3)_2$						⊕							(119)
β-Benzilyloxyethyl-dimethylamyl	 $(C_6H_5)_2COHCOO(CH_2)_2\underset{C_5H_{11}}{N^+}(CH_3)_2$						⊕							(119)
β-Acetoxyethyldi-methylbenzyl........	 $CH_3COO(CH_2)_2\underset{CH_2C_6H_5}{N^+}(CH_3)_2$		++		⊕	⊕		Br	M	750	SC			(108)

TABLE 4—*Continued*

CHOLINE DERIVATIVE	STRUCTURE OF CATION	PHARMACOLOGICAL ACTION						TOXIC DOSES		PARALYZING DOSE	REFERENCES
		Curariform action	Muscarinic action	Nicotinic action	Stimulating nicotinic action	Paralyzing nicotinic action	Atropine action	Mice	Miscellaneous		
								mg./kg.	*mg./kg.*	*mg./kg.*	
(α-Methyl-β-phenyl-β-hydroxyethyl)dimethylbenzyl.......	 $C_6H_5CHOH\underset{\underset{H_3C}{\vert}}{C}H\underset{\underset{CH_2C_6H_5}{\vert}}{C}HN^+(CH_3)_2$		⊕		++						(140)
γ-Benzilyloxypropyldimethylethyl.......	 $(C_6H_5)_2COHCOO(CH_2)_3\underset{\underset{C_2H_5}{\vert}}{N^+}(CH_3)_2$						⊕	Cl 50 90 IP Cl 50 550 SC			(119)
β-(Dibutylcarbamyloxy)ethyldimethylethyl...........	 $(C_4H_9)_2NCOO(CH_2)_2\overset{\overset{C_2H_5}{\vert}}{N^+}(CH_3)_2$		−			−	⊕				(155)
β-(p-Aminobenzoyloxy)ethylmethyldiethyl...............		⊕		⊕							(83, 84)

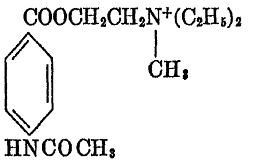
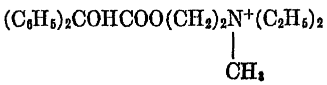
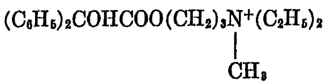
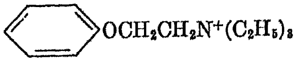
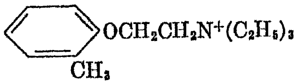
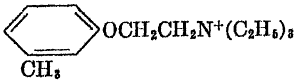
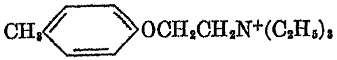
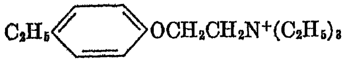
β-(*p*-Acetaminobenzoyloxy)ethylmethyldiethyl	 $p\text{-}CH_3CONHC_6H_4COOCH_2CH_2N^+(CH_3)(C_2H_5)_2$	+		⊕							(83, 84)
β-Benzilyloxyethylmethyldiethyl.......	 $(C_6H_5)_2COHCOO(CH_2)_2N^+(CH_3)(C_2H_5)_2$						⊕	Cl $\underline{50}$ 130 SC Cl $\underline{50}$ 625 IP			(119)
γ-Benzilyloxypropylmethyldiethyl	 $(C_6H_5)_2COHCOO(CH_2)_3N^+(CH_3)(C_2H_5)_2$						⊕	Cl $\underline{50}$ 650 SC			(119)
β-Hydroxyethyltriethyl...............	$HOCH_2CH_2N^+(C_2H_5)_3$							Cl M 70 SC			(116)
β-Acetoxyethyltriethyl...............	$CH_3COOCH_2CH_2N^+(C_2H_5)_3$		−		−	++		Br M 100 SC			(108)
β-Benzoyloxyethyltriethyl	$C_6H_5COO(CH_2)_2N^+(C_2H_5)_3$							Cl M 280 SC			(116)
β-Benzilyloxyethyltriethyl	$(C_6H_5)_2COHCOO(CH_2)_2N^+(C_2H_5)_3$						⊕	Br $\underline{50}$ 150 SC			(119)
β-Methoxyethyltriethyl...............	$CH_3OCH_2CH_2N^+(C_2H_5)_3$		−		−	−		I M 100 SC			(112)

TABLE 4—*Continued*

CHOLINE DERIVATIVE	STRUCTURE OF CATION	PHARMACOLOGICAL ACTION						TOXIC DOSES		PARALYZING DOSE	REFERENCES
		Curariform action	Muscarinic action	Nicotinic action	Stimulating nicotinic action	Paralyzing nicotinic action	Atropine action	Mice	Miscellaneous		
								mg./kg.	*mg./kg.*	*mg./kg.*	
β-Ethoxyethyltriethyl	$C_2H_5OCH_2CH_2N^+(C_2H_5)_3$		—		—	—		I M 320 SC			(112)
β-Butoxyethyltriethyl	$C_4H_9OCH_2CH_2N^+(C_2H_5)_3$	—	—		+	⊕		I M 230 SC			(112)
β-Phenoxyethyltriethyl			—			⊕		I M 180 SC			(112)
β-(2-Methylphenoxy)-ethyltriethyl			—		—	⊕		Br M 210 SC			(114)
β-(3-Methylphenoxy)-ethyltriethyl.			—		—	⊕		Br M 25 SC			(114)
β-(4-Methylphenoxy)-ethyltriethyl.			—		—	⊕		Br M 70 SC			(114)
β-(4-Ethylphenoxy)-ethyltriethyl.			—		—	⊕		Br M 90 SC			(114)

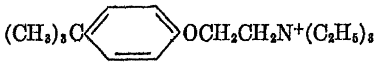
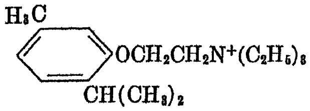
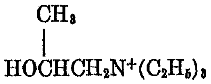
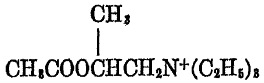
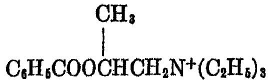
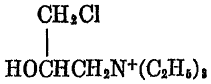
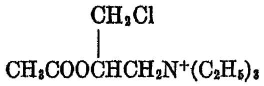
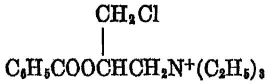
β-(4-*tert*-Butylphenoxy)ethyltriethyl			—		—	⊕		Br	M	35	SC			(114)
β-(2-Isopropyl-5-methylphenoxy)ethyltriethyl			—		—	⊕		Br	M	190	SC			(114)
β-Hydroxypropyltriethyl	 $\overset{CH_3}{HOCH}CH_2N^+(C_2H_5)_3$							Cl	M	180	SC			(116)
β-Acetoxypropyltriethyl	 $CH_3COO\overset{CH_3}{CH}CH_2N^+(C_2H_5)_3$							Cl	M	101	SC			(116)
(β-Benzoyloxypropyl)triethyl	 $C_6H_5COO\overset{CH_3}{CH}CH_2N^+(C_2H_5)_3$							Cl	M	320	SC			(116)
(β-Hydroxy-γ-chloropropyl)triethyl	 $\overset{CH_2Cl}{HOCH}CH_2N^+(C_2H_5)_3$							Cl	M	370	SC			(116)
(β-Acetoxy-γ-chloropropyl)triethyl	 $CH_3COO\overset{CH_2Cl}{CH}CH_2N^+(C_2H_5)_3$							Cl	M	209	SC			(116)
(β-Benzoyloxy-γ-chloropropyl)triethyl	 $C_6H_5COO\overset{CH_2Cl}{CH}CH_2N^+(C_2H_5)_3$							Cl	M	122	SC			(116)

TABLE 4—*Continued*

CHOLINE DERIVATIVE	STRUCTURE OF CATION	PHARMACOLOGICAL ACTION						TOXIC DOSES		PARALYZING DOSE	REFERENCES
		Curariform action	Muscarinic action	Nicotinic action	Stimulating nicotinic action	Paralyzing nicotinic action	Atropine action	Mice	Miscellaneous		
								mg./kg.	*mg./kg.*	*mg./kg.*	
β,γ-Dihydroxypropyltriethyl....	$HO\overset{\displaystyle CH_2OH}{\overset{\vert}{C}}HCH_2N^+(C_2H_5)_3$							Cl M 620 SC			(116)
β,γ-Diacetoxypropyltriethyl.	$CH_3COO\overset{\displaystyle CH_2OCOCH_3}{\overset{\vert}{C}}HCH_2N^+(C_2H_5)_3$							Cl M 460 SC			(116)
β,γ-Dibenzoyloxypropyltriethyl..........	$C_6H_5COO\overset{\displaystyle CH_2OCOC_6H_5}{\overset{\vert}{C}}HCH_2N^+(C_2H_5)_3$							Cl M 150 SC			(116)
Methoxymethyltriethyl...............	$CH_3OCH_2N^+(C_2H_5)_3$		–		–	–		I M 85 SC			(112)
Ethoxymethyltriethyl...............	$C_2H_5OCH_2N^+(C_2H_5)_3$	⊕	–		–	⊕		I M 100 SC			(112)
Alloxymethyltriethyl..	$CH_2{=}CHCH_2OCH_2N^+(C_2H_5)_3$	++	–		–	++		I M 120 SC			(112)
β-Benzilyloxyethyldiethylpropyl.......	$(C_6H_5)_2COHCOO(CH_2)_2\underset{\underset{\displaystyle C_3H_7}{\vert}}{N}{}^+(C_2H_5)_2$						⊕				(119)

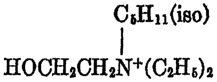
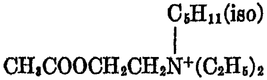
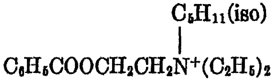
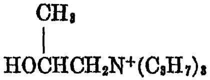
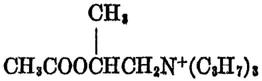
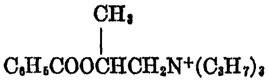
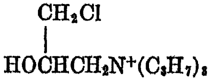
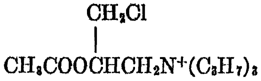
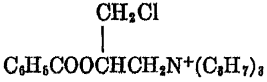
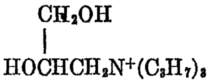
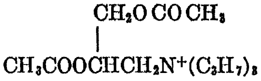
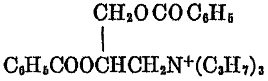
β-Hydroxyethyldi-ethylisoamyl........	 $HOCH_2CH_2\overset{\overset{C_5H_{11}(iso)}{\vert}}{N^+}(C_2H_5)_2$							Cl	M	630	SC			(116)
β-Acetoxyethyldi-ethylisoamyl........	 $CH_3COOCH_2CH_2\overset{\overset{C_5H_{11}(iso)}{\vert}}{N^+}(C_2H_5)_2$							Cl	M	400	SC			(116)
β-Benzoyloxyethyldi-ethylisoamyl........	 $C_6H_5COOCH_2CH_2\overset{\overset{C_5H_{11}(iso)}{\vert}}{N^+}(C_2H_5)_2$							Cl	M	1200	SC			(116)
β-Hydroxyethyltripropyl................	$HOCH_2CH_2N^+(C_3H_7)_3$							Cl	M	170	SC			(116)
β-Benzoyloxyethyltripropyl...	$C_6H_5COOCH_2CH_2N^+(C_3H_7)_3$							Cl	M	180	SC			(116)
β-Hydroxypropyltripropyl......	 $HO\overset{\overset{CH_3}{\vert}}{C}HCH_2N^+(C_3H_7)_3$							Cl	M	110	SC			(116)
β-Acetoxypropyltripropyl..............	 $CH_3COO\overset{\overset{CH_3}{\vert}}{C}HCH_2N^+(C_3H_7)_3$							Cl	M	160	SC			(116)
β-Benzoyloxypropyltripropyl........ ...	 $C_6H_5COO\overset{\overset{CH_3}{\vert}}{C}HCH_2N^+(C_3H_7)_3$							Cl	M	52	SC			(116)
(β-Hydroxy-γ-chloropropyl)tripropyl	 $HO\overset{\overset{CH_2Cl}{\vert}}{C}HCH_2N^+(C_3H_7)_3$							Cl	M	65	SC			(116)

TABLE 4—*Continued*

CHOLINE DERIVATIVE [1, 2]	STRUCTURE OF CATION	PHARMACOLOGICAL ACTION						TOXIC DOSES		PARALYZING DOSE	REFERENCES
		Curariform action	Muscarinic action	Nicotinic action	Stimulating nicotinic action	Paralyzing nicotinic action	Atropine action	Mice	Miscellaneous		
								mg./kg.	mg./kg.	mg./kg.	
(β-Acetoxy-γ-chloropropyl)tripropyl.....	 $\mathrm{CH_3COO\overset{\overset{CH_2Cl}{\vert}}{C}HCH_2N^+(C_3H_7)_3}$							Cl M 170 SC			(116)
(β-Benzoyloxy-γ-chloropropyl)tripropyl.	 $\mathrm{C_6H_5COO\overset{\overset{CH_2Cl}{\vert}}{C}HCH_2N^+(C_3H_7)_3}$							Cl M 60 SC			(116)
β,γ-Dihydroxypropyltripropyl	 $\mathrm{HO\overset{\overset{CH_2OH}{\vert}}{C}HCH_2N^+(C_3H_7)_3}$							Cl M 250 SC			(116)
β,γ-Diacetoxypropyltripropyl	 $\mathrm{CH_3COO\overset{\overset{CH_2OCOCH_3}{\vert}}{C}HCH_2N^+(C_3H_7)_3}$							Cl M 200 SC			(116)
β,γ-Dibenzoyloxypropyltripropyl..	 $\mathrm{C_6H_5COO\overset{\overset{CH_2OCOC_6H_5}{\vert}}{C}HCH_2N^+(C_3H_7)_3}$							Cl M 100 SC			(116)
β-Hydroxyethyltriamyl.........	$\mathrm{HOCH_2CH_2N^+(C_5H_{11})_3}$							Cl M 150 SC			(116)
β-Acetoxyethyltriamyl...............	$\mathrm{CH_3COOCH_2CH_2N^+(C_5H_{11})_3}$							Cl M 145 SC			(116)

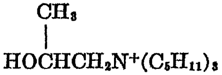
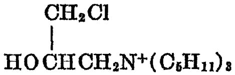
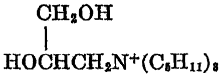
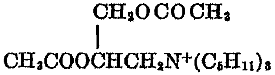
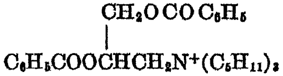
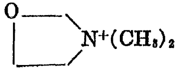
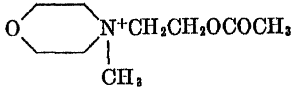
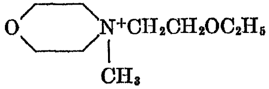
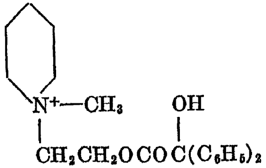
β-Benzoyloxyethyltriamyl	$C_6H_5COOCH_2CH_2N^+(C_5H_{11})_3$							Cl	M	36	SC			(116)
β-Hydroxypropyltriamyl	 $\overset{\displaystyle CH_3}{\overset{\vert}{HOCH}}CH_2N^+(C_5H_{11})_3$							Cl	M	90	SC			(116)
β-Acetoxypropyltriamyl	$CH_3COO\overset{\displaystyle CH_3}{\overset{\vert}{CH}}CH_2N^+(C_5H_{11})_3$							Cl	M	150	SC			(116)
β-Benzoyloxypropyltriamyl	$C_6H_5COO\overset{\displaystyle CH_3}{\overset{\vert}{CH}}CH_2N^+(C_5H_{11})_3$							Cl	M	38	SC			(116)
(β-Hydroxy-γ-chloropropyl)triamyl	 $HO\overset{\displaystyle CH_2Cl}{\overset{\vert}{CH}}CH_2N^+(C_5H_{11})_3$							Cl	M	210	SC			(116)
(β-Acetoxy-γ-chloropropyl)triamyl	$CH_3COO\overset{\displaystyle CH_2Cl}{\overset{\vert}{CH}}CH_2N^+(C_5H_{11})_3$							Cl	M	150	SC			(116)
(β-Benzoyloxy-γ-chloropropyl)triamyl	$C_6H_5COO\overset{\displaystyle CH_2Cl}{\overset{\vert}{CH}}CH_2N^+(C_5H_{11})_3$							Cl	M	39	SC			(116)
β,γ-Dihydroxypropyltriamyl	 $HO\overset{\displaystyle CH_2OH}{\overset{\vert}{CH}}CH_2N^+(C_5H_{11})_3$							Cl	M	400	SC			(116)
β,γ-Diacetoxypropyltriamyl	 $CH_3COO\overset{\displaystyle CH_2OCOCH_3}{\overset{\vert}{CH}}CH_2N^+(C_5H_{11})_3$							Cl	M	250	SC			(116)
β,γ-Dibenzoyloxypropyltriamyl	 $C_6H_5COO\overset{\displaystyle CH_2OCOC_6H_5}{\overset{\vert}{CH}}CH_2N^+(C_5H_{11})_3$							Cl	M	144	SC			(116)

TABLE 4—*Continued*

CHOLINE DERIVATIVE	STRUCTURE OF CATION	PHARMACOLOGICAL ACTION						TOXIC DOSES		PARALYZING DOSE	REFERENCES
		Curariform action	Muscarinic action	Nicotinic action	Stimulating nicotinic action	Paralyzing nicotinic action	Atropine action	Mice	Miscellaneous		
								mg./kg.	*mg./kg.*	*mg./kg.*	
Tetra(β-hydroxyethyl)	$N^+(CH_2CH_2OH)_4$		++		–	–		Cl M > 1500 SC			(108)
β-Acetoxyethyltri(β-hydroxyethyl)	$CH_2CH_2OCOCH_3$ | $N^+(CH_2CH_2OH)_3$		–		–	–					(108)
Dimethyloxazolium		⊕									(35)
β-Acetoxyethylmethylmorpholinium			+++		–						(140)
β-Ethoxyethylmethylmorpholinium			⊕		⊕						(140)
β-Benzilyloxyethylmethylpiperidinium							⊕				(119)

Ammonium compounds related to sulfur derivatives of choline

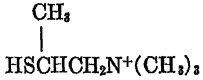
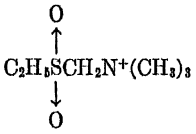
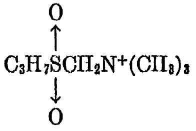
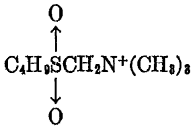
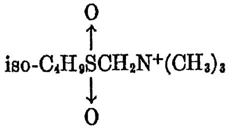
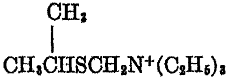
β-Sulfhydrylethyltrimethyl	$HSCH_2CH_2N^+(CH_3)_3$	++	+		−	++		Br M 26 SC			(110)
β-Acetylthioethyltrimethyl	$CH_3COSCH_2CH_2N^+(CH_3)_3$	++	+			++			Cats 0.15–2.2		(173, 179)
β-Sulfhydrylpropyltrimethyl	 $HS\overset{CH_3}{\overset{\vert}{C}}HCH_2N^+(CH_3)_3$	⊕	+			⊕					(87, 172)
Acetylthiomethyltrimethyl	$CH_3COSCH_2N^+(CH_3)_3$		++								(119)
Methylthiomethyltrimethyl	$CH_3SCH_2N^+(CH_3)_3$	⊕	++		−			I M 120 SC			(110)
Ethylthiomethyltrimethyl	$C_2H_5SCH_2N^+(CH_3)_3$		++		++	−		Cl M 40 SC			(110)
Propylthiomethyltrimethyl	$C_3H_7SCH_2N^+(CH_3)_3$		++		++			I M 66 SC			(110)
Isopropylthiomethyltrimethyl	iso-$C_3H_7SCH_2N^+(CH_3)_3$	⊕	⊕		⊕			I M 66 SC			(110)
Butylthiomethyltrimethyl	$C_4H_9SCH_2N^+(CH_3)_3$		⊕		⊕			I M 80 SC			(110)
Isobutylthiomethyltrimethyl	iso-$C_4H_9SCH_2N^+(CH_3)_3$		++		⊕			I M 67 SC			(110, 112)

TABLE 4—*Concluded*

CHOLINE DERIVATIVE	STRUCTURE OF CATION	PHARMACOLOGICAL ACTION						TOXIC DOSES		PARALYZING DOSE	REFERENCES
		Curariform action	Muscarinic action	Nicotinic action	Stimulating nicotinic action	Paralyzing nicotinic action	Atropine action	Mice	Miscellaneous		
								mg./kg.	mg./kg.	mg./kg.	
Ethylsulfonylmethyltrimethyl	 $C_2H_5\overset{\overset{O}{\uparrow}}{\underset{\underset{O}{\downarrow}}{S}}CH_2N^+(CH_3)_3$		+					SO_4 M 60 SC			(110)
Propylsulfonylmethyltrimethyl	 $C_3H_7\overset{\overset{O}{\uparrow}}{\underset{\underset{O}{\downarrow}}{S}}CH_2N^+(CH_3)_3$		+					SO_4 M 50 SC			(110)
Butylsulfonylmethyltrimethyl...	 $C_4H_9\overset{\overset{O}{\uparrow}}{\underset{\underset{O}{\downarrow}}{S}}CH_2N^+(CH_3)_3$		+					SO_4 M 28 SC			(110)
Isobutylsulfonylmethyltrimethyl...	 iso-$C_4H_9\overset{\overset{O}{\uparrow}}{\underset{\underset{O}{\downarrow}}{S}}CH_2N^+(CH_3)_3$							SO_4 M 43 SC			(110)

Methylthiomethyltriethyl	$CH_3SCH_2N^+(C_2H_5)_3$	++	−		−	++		I	M	80	SC			(112)
Ethylthiomethyltriethyl	$C_2H_5SCH_2N^+(C_2H_5)_3$		−		−			I	M	120	SC			(112)
Isopropylthiomethyltriethyl	 $CH_3\overset{\overset{CH_3}{\vert}}{C}HSCH_2N^+(C_2H_5)_3$	⊕	−		−	⊕		I	M	95	SC			(112)
Isobutylthiomethyltriethyl	iso-$C_4H_9SCH_2N^+(C_2H_5)_3$	++	−		−	++		I	M	95	SC			(112)

possess all, none, or varying combinations of these actions. Esterification of the hydroxyl group greatly increases the muscarinic action. Acetylcholine and acetyl-β-methylcholine have such effective muscarinic action that they have been used clinically in the treatment of various diseases, particularly those of blood vessels (74). Carbaminoylcholine is less readily hydrolyzed in the body than the above esters, and therefore has a more prolonged action and is effective orally.

Unna and coworkers (213) reported that carbaminoylcholine in extremely small doses greatly enhances and prolongs the curarizing effect of β-erythroidine.

The alkyl ethers of choline have a somewhat more effective muscarinic action than choline but are less effective than the esters. The aromatic ethers are devoid of muscarinic action and have very marked nicotinic actions.

A methyl group in the α- or β-position on the hydroxyethyl chain seems to have little effect on the activity. Acetyl-β-methylcholine is as effective as acetylcholine and has a more prolonged action, since it is somewhat less readily hydrolyzed. Other alkyl groups in the β-position abolish the nicotinic, reduce the muscarinic, and enhance the curare action, particularly in the case of the choline ethers. Derivatives containing a phenyl group in the hydroxyethyl chain, such as ephedrine derivatives, have only weak nicotinic and no muscarinic activity.

The formocholines are somewhat less active physiologically than the corresponding choline derivatives. γ-Homocholine has a greater muscarinic action than choline itself. The various derivatives of γ-homocholine, however, seem to be less effective than the corresponding derivatives of choline.

Benzilyl derivatives of choline in which one or more of the methyl groups on the nitrogen has been replaced by another alkyl group have atropine-like actions. Choline derivatives with the three methyl groups replaced by ethyl, propyl, and butyl groups lack both muscarinic and stimulating nicotinic actions. The ethers of the triethyl derivatives are reported to have only curare activity (74).

The replacing of the oxygen of choline with sulfur to form thiocholine greatly enhances the curare and paralyzing nicotinic actions and abolishes the stimulating nicotinic action. The ethers of the thioformocholine derivatives containing three ethyl groups on the nitrogen possess marked curare actions. The isobutyl ether has a very powerful but brief curare action (112).

5. Betaine derivatives and analogues (table 5)

Betaine itself is pharmacologically inert, but its esters have marked physiological action, chiefly muscarinic with some nicotinic. Replacement of the three methyl groups on the nitrogen in the betaine esters with ethyl, propyl, butyl, and other alkyl groups abolishes the muscarinic action. Thus, as was true in the tetraalkylammonium derivatives, the methyl groups on the nitrogen appear to play a part in causing muscarinic action. The amide of betaine possesses both muscarinic and nicotinic actions; substitution on the nitrogen of the amide diminishes the muscarinic action.

Very few data are available on the curare action of the betaine derivatives. Betaine itself and true betaine-type compounds, such as benzbetaine, the methyl betaine of nicotinic acid, tryptophan betaine, taurobetaine, and thiohistidine betaine, are pharmacologically inert. The fact that they do not exhibit a curare action may be due to the quaternary nitrogen not being a free ion, since a negative charge is present in the same molecule. Some of the esters of substituted betaines do have marked curare action, and these esters are onium ions of the ordinary type.

6. Diammonium compounds (table 6)

The few compounds of this type which have been reported have only weak pharmacological actions.

B. ARYLALKYLAMMONIUM COMPOUNDS

1. Aryltrialkylammonium compounds (table 7)

Aryltrialkylammonium compounds exhibit muscarinic, nicotinic, and weak curare actions. The replacement of an alkyl group on a quaternary nitrogen with an aryl group reduces the curare activity.

2. Prostigmine derivatives and analogues (table 8)

Prostigmine is a synthetic compound which is used as a physostigmine substitute in the treatment of eye and intestinal disorders. Its pharmacological action is due to the inhibition of cholinesterase in body fluids and tissues, thus preventing enzymatic hydrolysis of acetylcholine. Its effect on skeletal muscle in small doses is opposite to that of curare; indeed, it has been found to be an antagonist to curare paralysis (74), with the result that the effects of too large a dose of curare can be alleviated by injection of prostigmine.

Large doses of prostigmine, however, have been found to cause a peripheral paralysis similar to that of curare. Rosenblueth and Morison (186a) postulated that the cholinesterase inhibition of prostigmine allowed the acetylcholine formed at the myoneural junction to build up to concentrations above which the muscle does not respond (see page 287 for a discussion of their theories).

The cholinesterase inhibition of prostigmine is attributed to the carbamyl group. Stedman (199, 200) showed that the urethans of the isomeric dimethylaminophenols and of the isomeric hydroxybenzyldimethylamines possess miotic activity, which is a result of cholinesterase inhibition. He found that conversion of the tertiary bases of the dimethylaminophenol derivatives to the quaternary compounds intensifies the miotic action of the meta compounds and abolishes the actions of the ortho and para compounds. In the benzyl derivatives, the conversion to the quaternary compounds increases the miotic action of the ortho derivative, diminishes that of the meta, and abolishes that of the para compound. Stedman, Schweitzer, and Wright (201) reported that the tertiary bases are central convulsants, but the quaternary compounds are central depressants.

TABLE 5

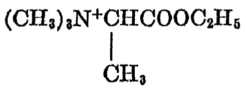
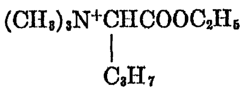
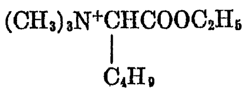
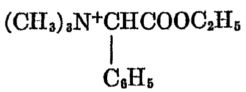
Alkylammonium compounds

Betaine derivatives and analogues

AMMONIUM COMPOUND	STRUCTURE	CURARIFORM ACTION	MUSCARINIC ACTION	STIMULATING NICOTINIC ACTION	PARALYZING NICOTINIC ACTION	TOXIC DOSES MICE	REFERENCES
						mg./kg.	
Carboxymethyltrimethyl-...... (Betaine)	$(CH_3)_3N^+CH_2COO^-$	–	–	–		M 2000 SC Cl M 3000 SC	(103, 105, 116, 117, 211)
Carbomethoxymethyltrimethyl-	$(CH_3)_3N^+CH_2COOCH_3$		++	+	+	Br M 110 SC	(103, 178)
Carbethoxymethyltrimethyl-...	$(CH_3)_3N^+CH_2COOC_2H_5$		++	+	+	Br M 170 SC	(103, 108, 153)
Carbobutoxymethyltrimethyl-..	$(CH_3)_3N^+CH_2COOC_4H_9$		⊕	+	+	Br M 420 SC	(103)
Carbobenzoxymethyltrimethyl-	$(CH_3)_3N^+CH_2COOCH_2C_6H_5$		⊕	+	+	Br M 290 SC	(103)
Carboxymethyltriethyl-..... ..	$(C_2H_5)_3N^+CH_2COO^-$		+	–	+	Br M > 1500 SC	(108)
Carbomethoxymethyltriethyl-..	$(C_2H_5)_3N^+CH_2COOCH_3$		–	–	+	Br M 400 SC	(108, 178)
Carbethoxymethyltriethyl-.....	$(C_2H_5)_3N^+CH_2COOC_2H_5$		–	–	⊕	Br M 430 SC	(108)
Carboxymethyltripropyl-......	$(C_3H_7)_3N^+CH_2COO^-$		–	–	–	Br M > 2000 SC	(108)
Carbomethoxymethyltripropyl-	$(C_3H_7)_3N^+CH_2COOCH_3$		–	–	++	Br M 180 SC	(108)
Carbethoxymethyltripropyl.....	$(C_3H_7)_3N^+CH_2COOC_2H_5$		–	–	++	Br M 120 SC	(108)

Carbomethoxymethyltributyl-.	$(C_4H_9)_3N^+CH_2COOCH_3$		−	+++		Br M 90 SC	(108, 178)
Carbethoxymethyltributyl-....	$(C_4H_9)_3N^+CH_2COOC_2H_5$		−	+++	−	Br M 100 SC	(108, 178)
Carboxymethyltriisoamyl-.....	$(iso\text{-}C_5H_{11})_3N^+CH_2COO^-$		+	+	−	Br M 120 SC	(108)
Carbethoxymethyltriisoamyl-...	$(iso\text{-}C_5H_{11})_3N^+CH_2COOC_2H_5$		−	++	⊕	Br M 120 SC	(108)
Carboxymethyltri(β-hydroxyethyl)-	$(HOCH_2CH_2)_3N^+CH_2COO^-$		+	−	−	Br M > 1500 SC	(108)
Carbethoxymethyltri(β-hydroxyethyl)-.............	$(HOCH_2CH_2)_3N^+CH_2COOC_2H_5$		−	−	−	Br M > 1500 SC	(108)
Carbomethoxymethylbenzyldimethyl-	$(CH_3)_2\underset{\substack{\vert\\ CH_2C_6H_5}}{N^+}CH_2COOCH_3$		+	+	⊕	Br M 380 SC	(108)
Carbethoxymethylbenzyldimethyl-....................	$(CH_3)_2\underset{\substack{\vert\\ CH_2C_6H_5}}{N^+}CH_2COOC_2H_5$		++	++	⊕	Br M 730 SC	(108)
Carbomethoxymethyldibenzylmethyl-......	$(C_6H_5CH_2)_2\underset{\substack{\vert\\ CH_3}}{N^+}CH_2COOCH_3$					Br M 170 SC	(108)
Carbethoxymethyldibenzylmethyl-....................	$(C_6H_5CH_2)_2\underset{\substack{\vert\\ CH_3}}{N^+}CH_2COOC_2H_5$		+	⊕	⊕	Br M 32 SC	(108)

TABLE 5—*Continued*

AMMONIUM COMPOUND	STRUCTURE	CURARIFORM ACTION	MUSCARINIC ACTION	STIMULATING NICOTINIC ACTION	PARALYZING NICOTINIC ACTION	TOXIC DOSES MICE		REFERENCES
							mg./kg.	
(α-Carbethoxyethyl)trimethyl-..	 $(CH_3)_3N^+\underset{\substack{\mid\\ CH_3}}{CH}COOC_2H_5$	++	⊕	+	+	Br M	560 SC	(103)
(α-Carbethoxybutyl)trimethyl-	 $(CH_3)_3N^+\underset{\substack{\mid\\ C_3H_7}}{CH}COOC_2H_5$	++	⊕	+	+	Br M	260 SC	(103)
(α-Carbethoxyamyl)trimethyl-..	 $(CH_3)_3N^+\underset{\substack{\mid\\ C_4H_9}}{CH}COOC_2H_5$	++	⊕	+	+	Br M	220 SC	(103)
(α-Carbethoxybenzyl)trimethyl-	 $(CH_3)_3N^+\underset{\substack{\mid\\ C_6H_5}}{CH}COOC_2H_5$	++	⊕	+	+	Br M	170 SC	(103)
(γ-Carboxypropyl)trimethyl-.	$(CH_3)_3N^+CH_2CH_2CH_2COO^-$	⊕						(211)
Formylmethyltrimethyl- . .	$(CH_3)_3N^+CH_2CHO$		⊕					(14, 66)
Dimethoxymethyltrimethyl-	$(CH_3)_3N^+CH(OCH_3)_2$		+					(66)
Carbamylmethyltrimethyl- .	$(CH_3)_3N^+CH_2CONH_2$		++	+	+	Cl M	420 SC	(103, 105, 153)
N-Methylcarbamylmethyltrimethyl.....	$(CH_3)_3N^+CH_2CONHCH_3$		++	+	+	Cl M	420 SC	(105)

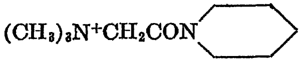
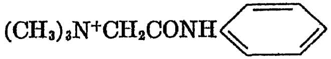
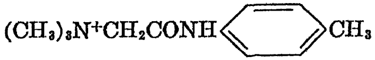
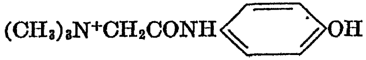
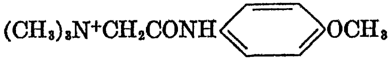
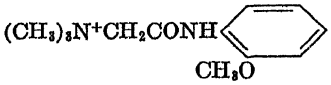
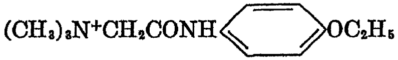
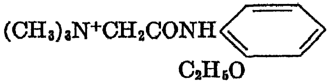
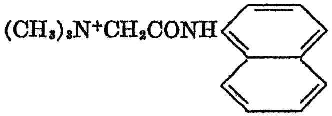
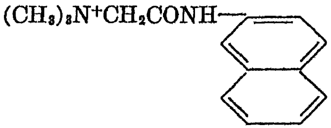
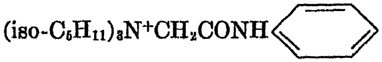
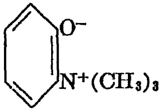
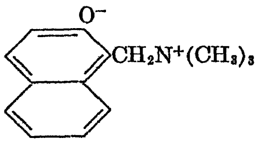
N-Ethylcarbamylmethyltrimethyl-	$(CH_3)_3N^+CH_2CONHC_2H_5$		++	+	+	Cl M	680 SC	(105)
N-Propylcarbamylmethyltrimethyl-	$(CH_3)_3N^+CH_2CONHC_3H_7$		–	+	⊕	Cl M	770 SC	(105)
N-Butylcarbamylmethyltrimethyl-	$(CH_3)_3N^+CH_2CONHC_4H_9$		–	+	⊕	Cl M	750 SC	(105)
Carbopiperidinomethyltrimethyl-			++	–	⊕	Cl M	370 SC	(105)
N-Phenylcarbamylmethyltrimethyl-			+	++	⊕	Cl M I M	670 SC 39 SC	(105, 111)
N-(*p*-Tolyl)carbamylmethyltrimethyl-			–	–	++	Cl M	440 SC	(105)
N-(*p*-Hydroxyphenyl)carbamylmethyltrimethyl-			–	⊕		Cl M	230 SC	(105)
N-(*p*-Methoxyphenyl)carbamylmethyltrimethyl-			–	–		Cl M	430 SC	(105)
N-(*o*-Methoxyphenyl)carbamylmethyltrimethyl-			–	–	⊕	Cl M	470 SC	(105)
N-(*p*-Ethoxyphenyl)carbamylmethyltrimethyl-			–	–		Cl M	350 SC	(105)
N-(*o*-Ethoxyphenyl)carbamylmethyltrimethyl-			–	–	⊕	Cl M	180 SC	(105)

TABLE 5—*Continued*

AMMONIUM COMPOUND	STRUCTURE	CURARIFORM ACTION	MUSCARINIC ACTION	STIMULATING NICOTINIC ACTION	PARALYZING NICOTINIC ACTION	TOXIC DOSES MICE	REFERENCES
						mg./kg.	
N-(α-Naphthyl)carbamylmethyltrimethyl-			–	–	⊕	Cl M 650 SC	(105)
N-(β-Naphthyl)carbamylmethyltrimethyl-			–	–	⊕	Cl M 260 SC	(105)
N-Phenylcarbamylmethyltriisoamyl-			–	–	–	Cl M 90 SC	(105)
Carbureidomethyltrimethyl-	$(CH_3)_3N^+CH_2CONHCONH_2$		++	⊕	+	Cl M 40 SC	(105)
Carb(phenylureido)methyltrimethyl-	$(CH_3)_3N^+CH_2CONHCONHC_6H_5$		+	–		Cl M 1000 SC	(105)
o-Hydroxyphenyltrimethyl- (Benzbetaine)		–	–	–	–		(88, 211)
2-Hydroxynaphthaltrimethyl-		–	–	–	–		(32)

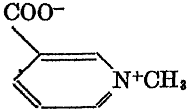
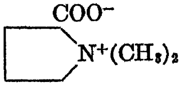
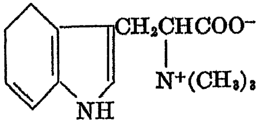
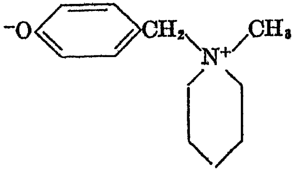
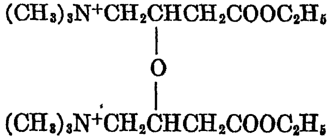
3-Carboxy-*N*-methylpyridinium.		—	—	—	—		(211)
2-Carboxy-*N*,*N*-dimethylpyrrolidinium..................		—	—	—	—		(211)
(Tryptophan betaine)..........		—	—	—	—		(211)
N-Methyl-*N*-(*p*-hydroxybenzyl) piperidinium............. ...		—	—	—	—		(32)
β-Sulfoethyltrimethyl-.......... (Taurobetaine)	$(CH_3)_3N^+CH_2CH_2SO_3^-$	—	—	—	—		(211)
(Thiohistidine betaine). ...	$C_9H_{15}O_2N_3S$	—	—	—	—		(211)

TABLE 6

Alkylammonium compounds

Diammonium compounds

DIAMMONIUM COMPOUND	STRUCTURE	PHARMACOLOGICAL ACTION				TOXIC DOSE CATS	PARALYZING DOSE FROGS	REFERENCES
		Curariform action	Muscarinic action	Stimulating nicotinic action	Other actions			
						mg./kg.	*mg./kg.*	
N,*N*,*N*,*N′*,*N′*,*N′*-Hexamethyldimethylene-	$(CH_3)_3N^+(CH_2)_2N^+(CH_3)_3$	+	⊕	⊕	Central depressant			(1, 193, 211)
N,*N*,*N*,*N′*,*N′*,*N′*-Hexamethyltrimethylene-	$(CH_3)_3N^+(CH_2)_3N^+(CH_3)_3$	+					Cl 300	(24)
N,*N*,*N*,*N′*,*N′*,*N′*-Hexamethyltetramethylene-	$(CH_3)_3N^+(CH_2)_4N^+(CH_3)_3$	⊕						(1, 211)
N,*N*,*N*,*N′*,*N′*,*N′*-Hexamethylpentamethylene-	$(CH_3)_3N^+(CH_2)_5N^+(CH_3)_3$	⊕						(1, 211)
N,*N*,*N*,*N′*,*N′*,*N′*-Hexamethyl-2-hydroxytrimethylene-	$(CH_3)_3N^+CH_2CHOHCH_2N^+(CH_3)_3$	–						(211)
Oblitin	 $(CH_3)_3N^+CH_2\underset{\underset{\underset{(CH_3)_3N^+CH_2CHCH_2COOC_2H_5}{\mid}}{O}}{\underset{\mid}{C}}HCH_2COOC_2H_5$	–				2000		(211)

Stevens and Beutel (202) showed that an alkyl group on the benzene ring makes the quaternary bases of the ortho and para compounds effective. It is remarkable that the methiodide of the dimethylcarbamyl derivative of *p*-dimethylaminophenol has a toxicity in mice of 120 mg./kg., whereas the corresponding compound with an isopropyl group on the ring in the position ortho to the nitrogen has a toxicity of 0.075 mg./kg. This represents an increase in toxicity by a factor of 1600.

Prostigmine has been used clinically in the treatment of infantile paralysis (124), but it is necessary to use atropine along with the prostigmine to suppress its muscarinic effects. Kabat and Knapp (124) reported that prostigmine acts at the spinal cord as well as at the myoneural junction.

C. HETEROCYCLIC AMMONIUM COMPOUNDS

1. Pyridinium compounds (table 9)

The alkylpyridinium salts possess weak curare activity, in some cases marked muscarinic activity, and in general, no nicotinic activity. The benzylpyridinium salt is the most effective of the pyridine derivatives. The ethyl- and propyl-pyridinium salts are less effective than the methyl derivatives. The isoamyl and cetyl derivatives have an action comparable to the methyl derivative.

The presence of an alkyl group on the ring seems to have little effect, as methyl-α-picolinium iodide has an activity comparable to that of methylpyridinium odide.

2. Piperidinium compounds (table 10)

Dimethylpiperidinium iodide is more effective in paralyzing the isolated nerve sartorius than is methylpyridinium iodide. Santesson and Koraen (190) observed that reduction of the pyridine ring increases the curare action, while Hunt and Renshaw (104) reported that reduction of the ring reduces the muscarinic and nicotinic actions and the toxicity.

3. Quinolinium compounds (table 11)

Unsubstituted alkylquinolinium salts possess a curare action but no muscarinic or nicotinic action. Increasing the length of the alkyl group increases the intensity of the curare action. Octylquinolinium iodide is half as effective as curarine in paralyzing the isolated nerve sartorius. .

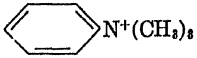
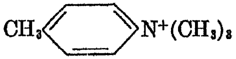
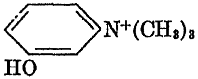
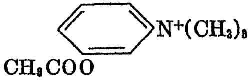
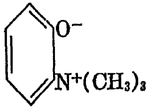
An alkyl group on the quinoline ring in the 2-, 4-, or 6-position renders the compound pharmacologically inert.

Dimethyl- and methylethyl-tetrahydroquinolinium salts are about equal in action to the ethylquinolinium salt and are more effective than the methylquinolinium salt. *N*,*N*-Dimethyl-6-methoxytetrahydroquinolinium chloride (dimethylthallinium chloride) is ten times more effective than methylquininium chloride. Since such a marked increase is not noted in the reduction of the unsubstituted quinolines, it seems probable that the methoxyl group acts to enhance the curare action.

TABLE 7

Arylalkylammonium compounds

Aryltrialkylammonium compounds

AMMONIUM COMPOUND	STRUCTURE	PHARMACOLOGICAL ACTION				TOXIC DOSES		PARALYZING DOSES			REFERENCES
		Curariform action	Muscarinic action	Stimulating nicotinic action	Paralyzing nicotinic action	Mice	Miscellaneous	Frogs	Minutes to paralyze isolated nerve sartorius Millimoles/ liter 1	10	
						mg./kg.	*mg./kg.*	*mg./kg.*	*minutes*		
Phenyltrimethyl-....		⊕	++	++	++	I 50 55 IP — 49 SC Cl 80 15 IV Cl 80 200–300 OS	Rabbits 80 OS	I 150	I 5.5		(3, 4, 24, 3 101, 11 120, 161,
p-Methylphenyltrimethyl-.......								I 80			(24)
m-Hydroxyphenyltrimethyl-						I 80 25–30 IV I 80 200–250 OS					(3)
m-Acetoxyphenyltrimethyl-........						CH_3SO_4 80 7.5–10 CH_3SO_4 80 1000 OS					(3)
o-Hydroxyphenyltrimethyl-.......		–	–	–	–						(88)

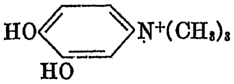
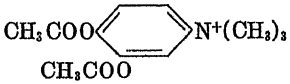
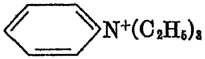
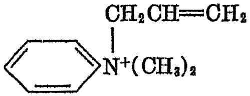
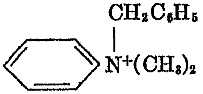
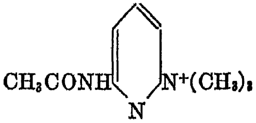
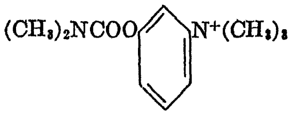
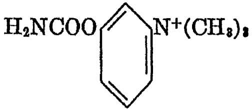
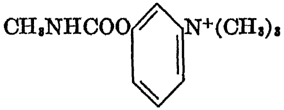
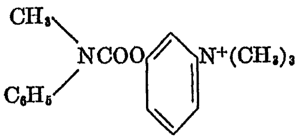
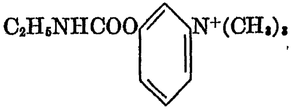
3,4-Dihydroxyphenyltrimethyl-				⊕						(211)
3,4-Diacetoxyphenyltrimethyl-.				⊕						(211)
Phenyltriethyl-		⊕								(211)
Phenyldimethylallyl-.		+								(211)
Phenyldimethylbenzyl-.		+						Cl 35		(32, 211)
(α-Acetaminopyridyl)trimethyl-. . . .								Cl 200		(24)

TABLE 8

Arylalkylammonium compounds

Prostigmine derivatives and analogues

AMMONIUM COMPOUND	STRUCTURE	PHARMACOLOGICAL ACTION		TOXIC DOSE MICE				REFERENCES
		Miotic action	Other actions			mg./kg.		
3-(Dimethylcarbamyloxy)phenyltrimethyl- (Prostigmine)		⊕	Weak curariform	I CH_3SO_4	50 80	0.55 0.5	 IV	(3, 74, 202)
3-(Carbamyloxy)phenyltrimethyl-		–		CH_3SO_4 CH_3SO_4	80 80	0.7 500	IV OS	(3)
3-(Methylcarbamyloxy)phenyltrimethyl-		⊕	Central depressant	Br I CH_3SO_4 CH_3SO_4	80 80 80 80	0.15 0.1 0.1 2.5	IV IV IV IV	(3, 201)
3-(Methylphenylcarbamyloxy)-phenyltrimethyl-			Central depressant	CH_3SO_4	80	3.5	IV	(3, 201)
3-(Ethylcarbamyloxy)phenyltrimethyl-				CH_3SO_4	80	1	IV	(3)

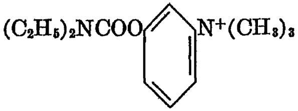
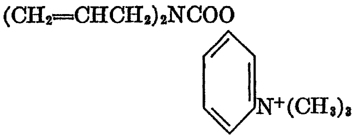
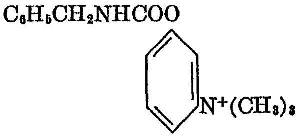
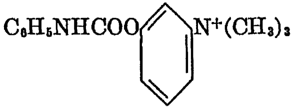
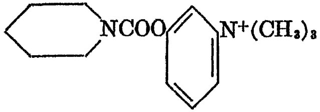
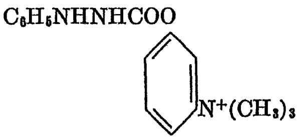
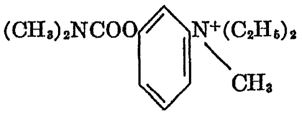
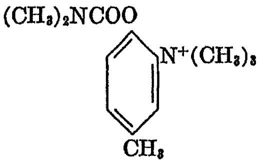
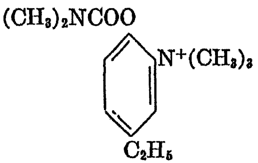
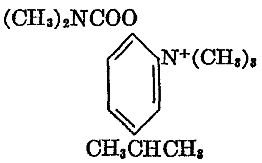
3-(Diethylcarbamyloxy)phenyl-trimethyl-.				CH_3SO_4	$\underline{80}$	8	IV	(3)
3-(Diallylcarbamyloxy)phenyltri-methyl-.......................				CH_3SO_4	$\underline{80}$	10	IV	(3)
3-(Benzylcarbamyloxy)phenyl-trimethyl-...				CH_3SO_4	$\underline{80}$	0.1	IV	(3)
3-(Phenylcarbamyloxy)phenyl-trimethyl-............				CH_3SO_4	$\underline{80}$	2	IV	(3)
3-(Pentamethylenecarbamyloxy)-phenyltrimethyl-				CH_3SO_4	$\underline{80}$	6	IV	(3)
3-(Phenylhydrazinoformyloxy)-phenyltrimethyl-..............				CH_3SO_4	$\underline{80}$	0.25	IV	(3)

TABLE 8—*Continued*

AMMONIUM COMPOUND	STRUCTURE	PHARMACOLOGICAL ACTION		TOXIC DOSE MICE	REFERENCES
		Miotic action	Other actions		
				mg./kg.	
3-(Dimethylcarbamyloxy)phenyldiethylmethyl-...........			Physostigmine action		(201)
2-(Dimethylcarbamyloxy)-5-methylphenyltrimethyl-.......				I $\underline{50}$ 2	(202)
2-(Dimethylcarbamyloxy)-5-ethylphenyltrimethyl-........				I $\underline{50}$ 1.25	(202)
2-(Dimethylcarbamyloxy)-5-isopropylphenyltrimethyl-...				I $\underline{50}$ 4.8	(202)

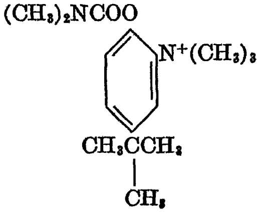
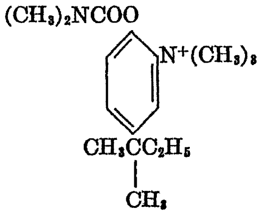
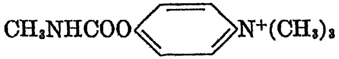
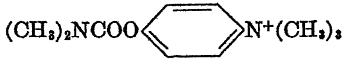
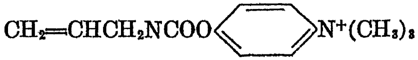
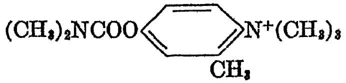
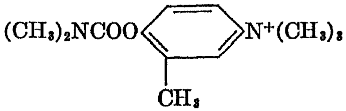
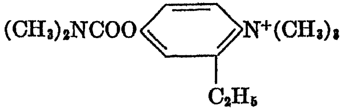
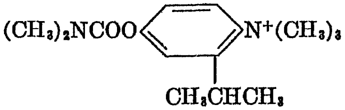
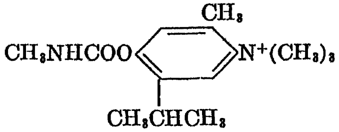
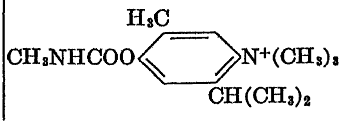
2-(Dimethylcarbamyloxy)-5-*tert*-butylphenyltrimethyl-				I	50	13.5		(202)
2-(Dimethylcarbamyloxy)-5-*tert*-amylphenyltrimethyl-				I	50	12		(202)
4-(Methylcarbamyloxy)phenyltrimethyl-				I	80	2	IV	(3)
4-(Dimethylcarbamyloxy)phenyltrimethyl-				I	50	120		(202)
4-(Allylcarbamyloxy)phenyltrimethyl-				CH_3SO_4	80	0.75	IV	(3)
4-(Dimethylcarbamyloxy)-2-methylphenyltrimethyl-				I	50	13		(202)

TABLE 8—*Continued*

AMMONIUM COMPOUND	STRUCTURE	PHARMACOLOGICAL ACTION		TOXIC DOSE MICE	REFERENCES
		Miotic action	Other actions		
				mg./kg.	
4-(Dimethylcarbamyloxy)-3-methylphenyltrimethyl-........				I $\underline{50}$ 6.5	(202)
4-(Dimethylcarbamyloxy)-2-ethylphenyltrimethyl-..........				I $\underline{50}$ 1.15	(202)
4-(Dimethylcarbamyloxy)-2-isopropylphenyltrimethyl-....				I $\underline{50}$ 0.075	(202)
4-(Methylcarbamyloxy)-2-methyl-5-isopropylphenyltrimethyl-....				I $\underline{50}$ 0.22	(202)
4-(Methylcarbamyloxy)-3-methyl-6-isopropylphenyltrimethyl-....				I $\underline{50}$ 0.09	(202)

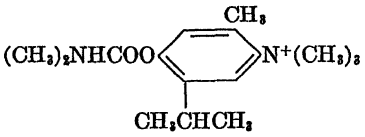
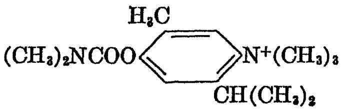
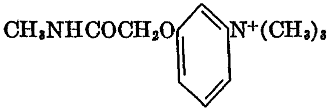
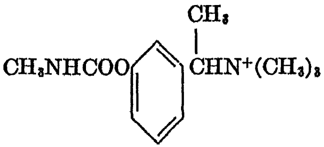
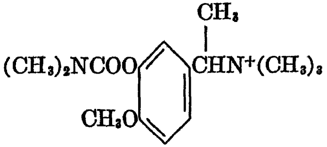
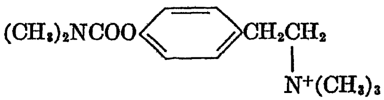
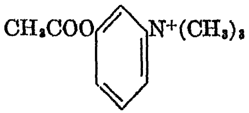
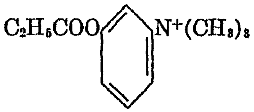
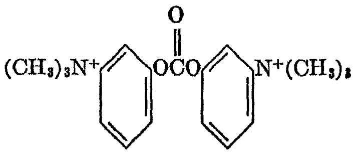
4-(Dimethylcarbamyloxy)-2-methyl-5-isopropylphenyltrimethyl-........				I	$\underline{50}$	0.72		(202)
4-(Dimethylcarbamyloxy)-3-methyl-6-isopropylphenyltrimethyl-........				I	$\underline{50}$	0.24		(202)
3-(Methylcarbamylmethoxy)-phenyltrimethyl-........			Central depressant	CH_3SO_4 CH_3SO_4	80 $\underline{80}$	7.5 1000	IV OS	(3, 201)
α-(3-Methylcarbamyloxyphenyl)-ethyltrimethyl-........ (Miotine)		++	Weak muscarinic					(201)
α-(3-Dimethylcarbamyloxy-4-methoxyphenyl)ethyltrimethyl-........				I	$\underline{80}$	5	IV	(3)
β-(4-Dimethylcarbamyloxyphenyl)ethyltrimethyl-........			Central depressant					(201)

TABLE 8—*Concluded*

AMMONIUM COMPOUND	STRUCTURE	PHARMACOLOGICAL ACTION		TOXIC DOSE MICE	REFERENCES
		Miotic action	Other actions		
				mg./kg.	
3-Acetoxyphenyltrimethyl-				CH$_3$SO$_4$ 80 7.5 IV CH$_3$SO$_4$ 80 1000 OS	(3)
3-Propionyloxyphenyltrimethyl-..		—		I 80 25 IV I 80 500 OS	(3, 201)
(Bis(3-trimethylammonium-phenyl)carbonate)...				CH$_3$SO$_4$ 80 12.5 IV CH$_3$SO$_4$ 80 1000 OS	(3)

4. Isoquinolinium compounds (table 12)

Hjort and coworkers (89–97) and Takase and coworkers (204–206) published a series of papers on the pharmacology of various substituted isoquinolines, dihydroisoquinolines, and tetrahydroisoquinolines. No mention was made of any peripheral curare paralysis. The effect of substituents on the toxicity and blood pressure was shown. In three homologous series of 2-alkyltetrahydroisoquinoline derivatives it was shown that the toxicity increases with increasing length of the 2-alkyl group. 6,7-Dihydroxy compounds are less toxic than 6,7-dimethoxy compounds. Substituents in the 6- and 7-positions have less effect on toxicity and blood pressure response than substituents on the nitrogen.

Takase and Sato (205) found that certain 2-methyldihydro- and 2-methyltetrahydro-isoquinoline derivatives have anesthetic and antispasmodic actions. Since the blood pressure effect of the compounds is not prevented by atropine (not a muscarinic action), the action must be on the central nervous system.

The paralyzing doses for frogs indicate that *N*-methylisoquinolinium chloride is less effective than *N*-methylquinolinium iodide. However, Santesson (189) reported that the order of intensity of curare paralysis is 1:2.5:3.75:25 for methylpyridinium, methylquinolinium, methylisoquinolinium, and dimethylthallinium chlorides, respectively.

Various workers (93, 206) have noted the similarity of action between isoquinolines and β-phenylethylamines, which may be regarded as the parent compound of isoquinolines. Further discussion of this observation and of other isoquinolines is included under isoquinoline alkaloids (see page 388).

5. Miscellaneous heterocyclic compounds (table 13)

Some pyrazolium salts have been reported to possess a curare action. These compounds also paralyze the central nervous system, possibly because of the secondary nitrogen present. Two isoxazolium salts have been reported to possess curare activity.

D. ALKALOIDS

1. Curare alkaloids (table 14)

Preparations from South American curare have a powerful and prolonged peripheral paralyzing action; the mechanism of the action has already been discussed (see page 287).

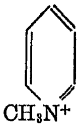
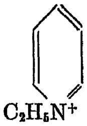
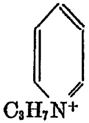
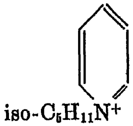
Boehm (12) isolated from tube curare the inactive, tertiary alkaloid curine in a crystalline form and assigned to it the formula $C_{18}H_{19}NO_3$. This formula was accepted by Späth, Leithe, and Ladeck (198), who proposed a benzyltetrahydroisoquinoline structure, which was later doubled to a bisbenzyltetrahydroisoquinoline by Späth and Kuffner (197) on the basis of molecular-weight determinations.

The active, amorphous alkaloid "tubocurarine" obtained by Boehm (12) from tube curare was obtained as a crystalline chloride by King (129). Since

TABLE 9

Heterocyclic ammonium compounds

Pyridinium compounds

AMMONIUM COMPOUND	STRUCTURE	PHARMACOLOGICAL ACTION				TOXIC DOSES		PARALYZING DOSES			REFERENCES
		Curariform action	Muscarinic action	Stimulating nicotinic action	Paralyzing nicotinic action	Mice	Miscellaneous	Frogs	Minutes to paralyze isolated nerve sartorius		
									Millimoles/liter 1	10	
						mg./kg.	*mg./kg.*	*mg./kg.*	*minutes*		
N-*M*ethylpyridinium	 CH_3N^+	⊕					Cats Cl 500 SC Frogs Cl 500	I 300 SC Cl 300–400	I	26	(121, 144, 211)
N-Ethylpyridinium	 $C_2H_5N^+$						Rabbits Cl 200 Frogs Cl 40	I 1500 SC	I 60		(121, 211)
N-Propylpyridinium	 $C_3H_7N^+$	⊕						I 600 SC			(144)
N-Isoamylpyridinium	 iso-$C_5H_{11}N^+$	⊕						I 300 SC			(144)

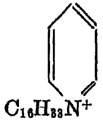
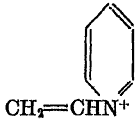
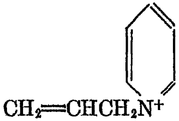
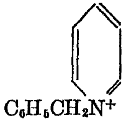
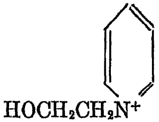
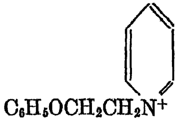
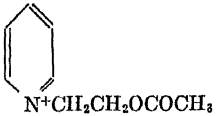
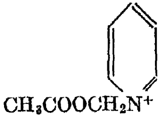
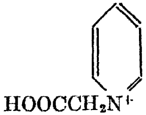
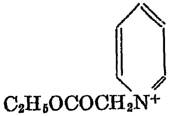
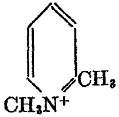
N-Cetylpyridinium	 $C_{16}H_{33}N^+$	⊕		⊕		Cl M 2 IP	Rabbits Cl M 20 IV Rats 50 30 IV 50 200 OS	Br 300			(24, 152 215)
N-Vinylpyridinium	 $CH_2{=}CHN^+$	⊕					Rabbits Cl 15 Frogs Cl 5				(211)
N-Allylpyridinium	 $CH_2{=}CHCH_2N^+$	⊕						I 1500 SC			(144)
N-Benzylpyridinium	 $C_6H_5CH_2N^+$							Cl 90 SC			(144)
N-(β-Hydroxyethyl)pyridinium	 $HOCH_2CH_2N^+$	⊕									(211)
N-(β-Phenoxyethyl)pyridinium	 $C_6H_5OCH_2CH_2N^+$	+	+			Br M 220 SC					(106)

TABLE 9—*Continued*

AMMONIUM COMPOUND	STRUCTURE	PHARMACOLOGICAL ACTION				TOXIC DOSES		PARALYZING DOSES			REFERENCES
		Curariform action	Muscarinic action	Stimulating nicotinic action	Paralyzing nicotinic action	Mice	Miscellaneous	Frogs	Minutes to paralyze isolated nerve sartorius		
									Millimoles/liter 1	10	
						mg./kg.	*mg./kg.*	*mg./kg.*	*minutes*		
N-(*β*-Acetoxyethyl)pyridinium			+++								(143)
N-Acetoxymethylpyridinium			++	+		Cl 130 SC					(101, 104)
N-Carboxymethylpyridinium			+	–	–	Br >2000 SC					(104)
N-Carbethoxymethylpyridinium			++		–	Br 370 SC					(101, 104)
N-Methyl-*α*-picolinium								I 300			(24)

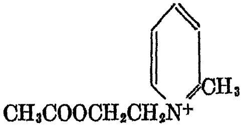
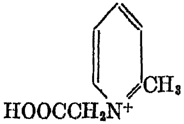
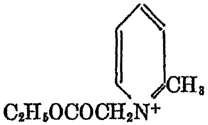
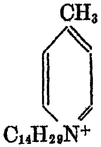
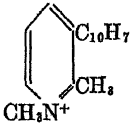
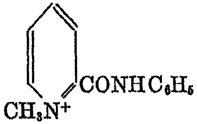
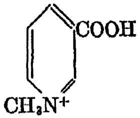
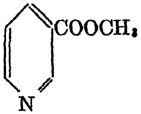
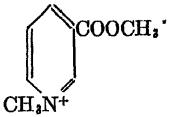
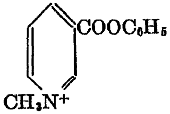
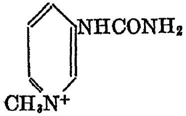
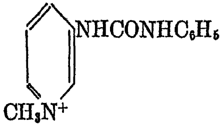
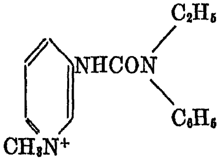
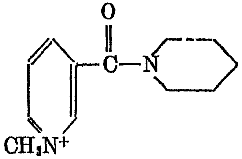
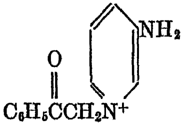
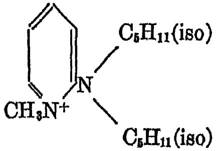
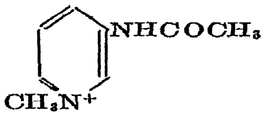
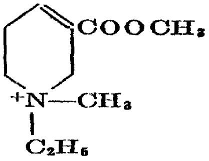
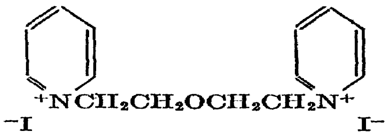
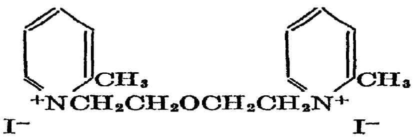
N-(β-Acetoxyethyl)-α-picolinium			+++								(143)
N-Carboxymethyl-α-picolinium		–				SO_4 M >1600 SC					(106)
N-Carbethoxymethyl-α-picolinium			–	–	+	Br 700 SC					(104)
N-Myristyl-γ-picolinium							Rats $\overline{50}$ 7.5 IP $\overline{50}$ 30 IV $\overline{50}$ 200 SC $\overline{50}$ 250 OS				(152)
N-Methyl-β-naphthyl-α-picolinium								Br 300			(24)
N-Methyl-α-(phenylcarbamyl)pyridinium		–	–	–	–	I M 1000 SC					(162)

TABLE 9—*Continued*

AMMONIUM COMPOUND	STRUCTURE	PHARMACOLOGICAL ACTION				TOXIC DOSES		PARALYZING DOSES			REFERENCES
		Curariform action	Muscarinic action	Stimulating nicotinic action	Paralyzing nicotinic action	Mice	Miscellaneous	Frogs	Minutes to paralyze isolated nerve sartorius Millimoles/liter 1	10	
						mg./kg.	*mg./kg.*	*mg./kg.*	*minutes*		
N-Methyl-β-carboxypyridinium								I 300			(24)
Methyl ester of nicotinic acid			++	−	−	>1000 SC					(104)
N-Methyl-β-carbomethoxypyridinium			++	−	−	I 600 SC					(104)
N-Methyl-β-carbophenoxypyridinium			−	+		I M 1000 SC					(106)
N-Methyl-β-carbamidopyridinium			+	−		I M 1400 SC					(106)

N-*M*ethyl-β-phenylcarbamidopyridinium			—	—		I M >1600 SC					(106)
N-Methyl-β-ethylphenylcarbamidopyridinium			—	—		I M 1350 SC					(106)
N-Methyl-β-carbopiperidinopyridinium		—	—	—	—	I M 440 SC					(106)
N-Phenacyl-β-aminopyridinium								Br 300			(24)
N-Methyl-α-diisoamylaminopyridinium								I 600			(144)

AMMONIUM COMPOUND	STRUCTURE	
N-Methyl-β-acetaminopyridinium		
N-Methyl-*N*-ethyl-β-carbomethoxytetrahydropyridinium		
N,*N*′-2,2′-Bis(pyridinium iodide) diethyl ether		
N,*N*′-2,2′-Bis(2-methylpyridinium iodide)diethyl ether		

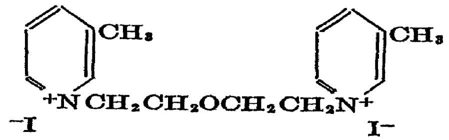
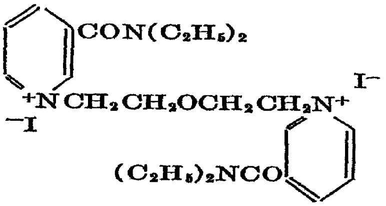
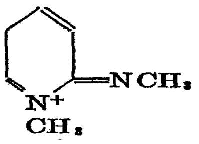
N,*N*′-2,2′-Bis(3-methylpyridinium iodide)diethyl ether		
N,*N*′-2,2′-Bis-(3,3′-bis(diethylcarbamyl)pyridinium iodide)-diethyl ether		
Methiodide of α-pyridonemethylimide		⊕

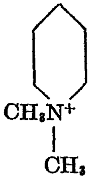
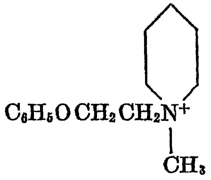
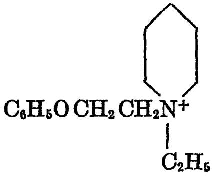
TABLE 9—*Concluded*

PHARMACOLOGICAL ACTION				TOXIC DOSES		PARALYZING DOSES			REFERE
Curariform action	Muscarinic action	Stimulating nicotinic action	Paralyzing nicotinic action	Mice	Miscellaneous	Frogs	Minutes to paralyze isolated nerve sartorius Millimoles/liter 1	10	
				mg./kg.	*mg./kg.*	*mg./kg.*	*minutes*		
+	−			I M 850 SC					(106)
	+++	−	+	Br M 65 SC					(104)
						238 EL			(160)
						227 EL			(160)
						185 EL			(160)
						>1900 EL			(160)
						I 300 SC			(144)

TABLE 10

Heterocyclic ammonium compounds

Piperidinium compounds

PIPERIDINIUM COMPOUND	STRUCTURE	PHARMACOLOGICAL ACTIONS					TOXIC DOSE MICE	MINUTES TO PARALYZE ISOLATED NERVE SARTORIUS 10 milli-moles/liter	REFERENCES
		Curariform action	Muscarinic action	Stimulating nicotinic action	Paralyzing nicotinic action	Atropine action			
							mg./kg.	*minutes*	
N,*N*-Dimethyl-		⊕						I 8	(121)
N-Methyl-*N*-(β-phenoxyethyl)-			−	−	+		I M 900 SC		(106)
N-Ethyl-*N*-(β-phenoxyethyl)-			−	−			Br M 160 SC		(106)

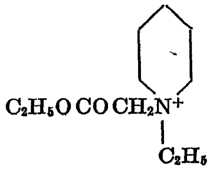
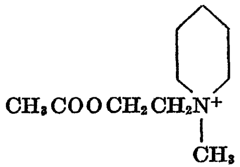
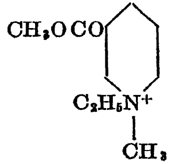
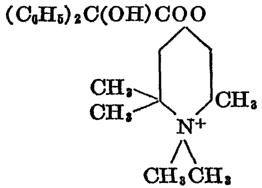
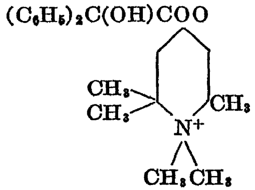
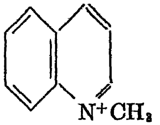
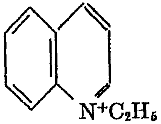
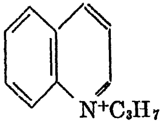
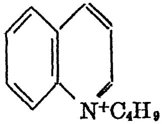
N-Carbethoxymethyl-*N*-ethyl-			+				Br M 180 SC		(104)
N-(β-Acetoxyethyl)-*N*-methyl-			++	–	–		I M 270 SC		(104)
3-Carbomethoxy-*N*-ethyl-*N*-methyl-			⊕				Br M 180 SC		(104)
4-Benzilyloxy-*N*,*N*,2,2,6-pentamethyl- (β-isomer)						⊕	Cl $\underline{50}$ 75 IP Cl $\underline{50}$ 325 SC Cl $\underline{50}$ 1000 OS		(119)
4-Benzilyloxy-*N*,*N*,2,2,6-pentamethyl- (α-Isomer)						⊕	Cl $\underline{50}$ 80 IP Cl $\underline{50}$ 325 SC		(119)

TABLE 11

Heterocyclic ammonium compounds

Quinolinium compounds

QUINOLINIUM COMPOUND	STRUCTURE	PHARMACOLOGICAL ACTION				TOXIC DOSE	PARALYZING DOSES			REFERENCES
		Curariform action	Muscarinic action	Stimulating nicotinic action	Paralyzing nicotinic action		Frogs	Isolated nerve sartorius Millimoles/liter 1	10	
						mg./kg.	*mg./kg.*	*minutes*		
N-Methyl-		⊕					I 300 340	I	9.25	(24, 121)
N-Ethyl-		+	–	–	–	Mice M 120 SC		I 14	4	(106, 121)
N-Propyl-		⊕						I 6		(121)
N-Butyl-		⊕						I 6		(121)

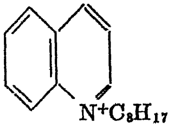
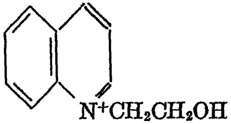
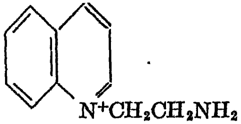
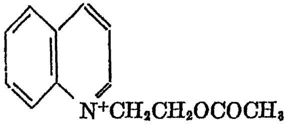
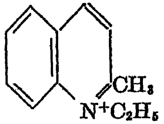
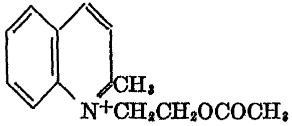
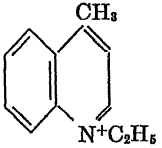
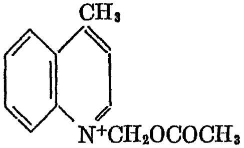
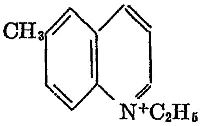
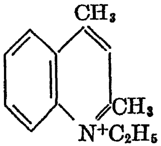
N-Octyl-		⊕						I 5.8		(121)
N-(β-Hydroxyethyl)-		⊕								(211)
N-(β-Aminoethyl)-						Rabbits Cl 27 IV				(211)
N-(β-Acetoxyethyl)-			+++							(143)
N-Ethyl-2-methyl-		–	–	–	–	Mice M 100 SC				(106)
N-(β-Acetoxyethyl)-2-methyl-			+++							(143)

TABLE 11—*Concluded*

QUINOLINIUM COMPOUND	STRUCTURE	PHARMACOLOGICAL ACTION				TOXIC DOSE	PARALYZING DOSES			REFERENCES
		Curariform action	Muscarinic action	Stimulating nicotinic action	Paralyzing nicotinic action		Frog	Isolated nerve sartorius Millimoles/liter		
								1	10	
						mg./kg.	*mg./kg.*	*minutes*		
N-Ethyl-4-methyl-		—	—	—	—	Mice M 120 SC				(106)
N-Acetoxymethyl-4-methyl-			—	—	—	Mice Br 280 SC				(104)
N-Ethyl-6-methyl-		—	—	—	—	Mice M 85 SC				(106)
N-Ethyl-2,4-dimethyl-		—	—	—	—	Mice M 110 SC				(106)

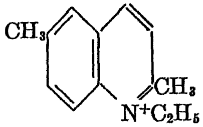
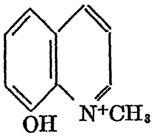
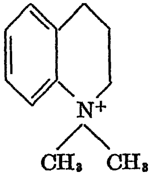
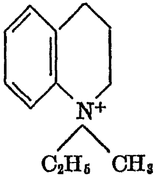
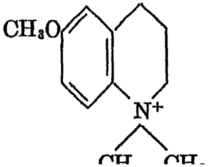
N-Ethyl-2,6-dimethyl-		—	—	—	—	Mice M 120 SC				(106)
N-Methyl-8-hydroxy-						Mice I 80 0.1 IV				(194)
(Diquinolyl dimethyl-sulfate)	Structure undetermined	⊕	—	—	—	Rabbits 30				(98, 211)
N,*N*-Dimethyltetrahydro-								I 12.25		(121)
N-Ethyl-*N*-methyltetrahydro-								I 20		(120)
N,*N*-Dimethyl-6-methoxytetrahydro- (Dimethylthallinium)		⊕								(190)

TABLE 12

Heterocyclic ammonium compounds

Isoquinolinium compounds

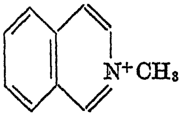
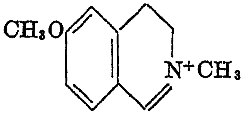
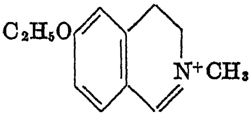
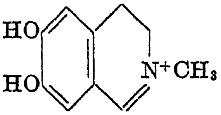
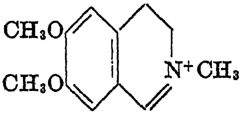
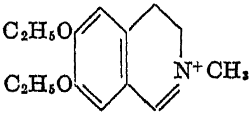
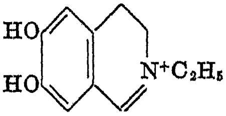
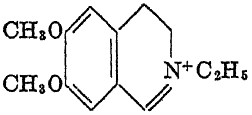
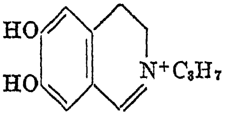
ISOQUINOLINIUM COMPOUND	STRUCTURE	PHARMACOLOGICAL ACTION		TOXIC DOSE MICE	PARALYZING DOSE FROGS	REFERENCES
		Curari-form action	Effect on blood pressure			
				mg./kg.	*mg./kg.*	
N-Methyl-		+			Cl 500	(190, 211)
N-Methyl-6-methoxy-3,4-dihydro-			d p	Cl 50 166 IP		(91)
N-Methyl-6-ethoxy-3,4-dihydro-			d p	Cl 50 184 IP		(91)
N-Methyl-6,7-dihydroxy-3,4-dihydro-			p	Cl 50 120 IP		(91)
N-Methyl-6,7-dimethoxy-3,4-dihydro-		⊕	p	Cl 50 92 IP		(91, 211)
N-Methyl-6,7-diethoxy-3,4-dihydro-			d	Cl 50 124 IP		(91)
N-Ethyl-6,7-dihydroxy-3,4-dihydro-			p	Cl 50 116 IP		(91)
N-Ethyl-6,7-dimethoxy-3,4-dihydro-			d p	Cl 50 99 IP		(91)
N-Propyl-6,7-dihydroxy-3,4-dihydro-			p	Cl 50 134 IP		(91)

TABLE 12—*Continued*

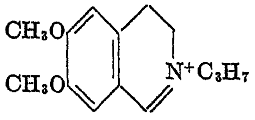
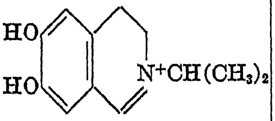
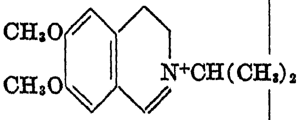
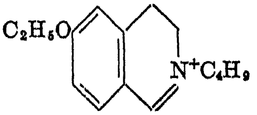
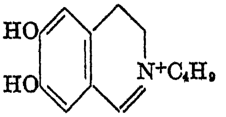
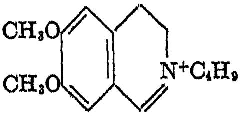
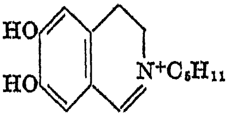
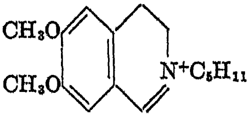
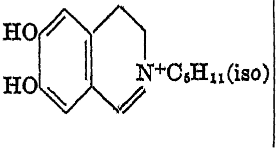
ISOQUINOLINIUM COMPOUND	STRUCTURE	PHARMACOLOGICAL ACTION		TOXIC DOSE MICE	PARALYZING DOSE FROGS	REFERENCES
		Curariform action	Effect on blood pressure			
				mg./kg.	*mg./kg.*	
N-Propyl-6,7-dimethoxy-3,4-dihydro-			d	Cl 50 73 IP		(91)
N-Isopropyl-6,7-dihydroxy-3,4-dihydro-			d p	Cl 50 109 IP		(91)
N-Isopropyl-6,7-dimethoxy-3,4-dihydro-			d	Cl 50 86 IP		(91)
N-Butyl-6-ethoxy-3,4-dihydro-			d			(91)
N-Butyl-6,7-dihydroxy-3,4-dihydro-			d p	Cl 50 179 IP		(91)
N-Butyl-6,7-dimethoxy-3,4-dihydro-			d	Cl 50 126 IP		(91)
N-Amyl-6,7-dihydroxy-3,4-dihydro-			d p	Cl 50 159 IP		(91)
N-Amyl-6,7-dimethoxy-3,4-dihydro-			d	Cl 50 108 IP		(91)
N-Isoamyl-6,7-dihydroxy-3,4-dihydro-			d	Cl 50 170 IP		(91)

TABLE 12—*Continued*

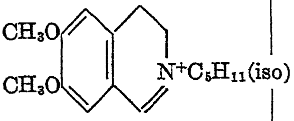
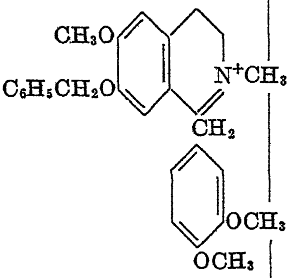
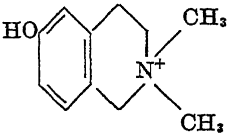
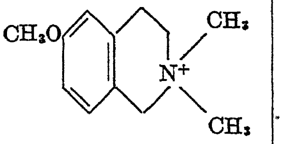
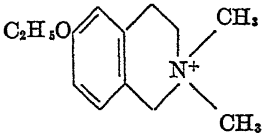
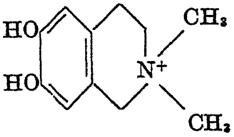
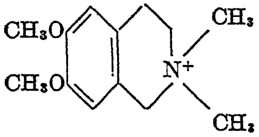
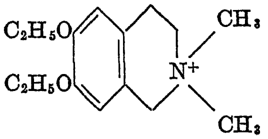
ISOQUINOLINIUM COMPOUND	STRUCTURE	PHARMACOLOGICAL ACTION		TOXIC DOSE MICE	PARALYZING DOSE FROGS	REFERENCES
		Curariform action	Effect on blood pressure			
				mg./kg.	*mg./kg.*	
N-Isoamyl-6,7-dimethoxy-3,4-dihydro-			d	Cl 50 130 IP		(91)
N-Methyl-6-methoxy-7-benzyloxy-1-(3,4-dimethoxybenzyl)-3,4-dihydro-	 CH_3O $C_6H_5CH_2O$ N^+CH_3 CH_2 OCH_3 OCH_3	⊕				(204)
N,*N*-Dimethyl-6-hydroxytetrahydro-			d p	Cl 50 25 IP		(90)
N,*N*-Dimethyl-6-methoxytetrahydro-			p	Cl 50 31 IP		(90)
N,*N*-Dimethyl-6-ethoxytetrahydro-			p	Cl 50 58 IP		(90)
N,*N*-Dimethyl-6,7-dihydroxytetrahydro-			d p	Cl 50 33 IP		(90)
N,*N*-Dimethyl-6,7-dimethoxytetrahydro-			p	Cl 50 20 IP		(90)

TABLE 12—*Concluded*

ISOQUINOLINIUM COMPOUND	STRUCTURE	PHARMACOLOGICAL ACTION		TOXIC DOSE MICE	PARALYZING DOSE FROGS	REFERENCES
		Curariform action	Effect on blood pressure			
				mg./kg.	*mg./kg.*	
N,*N*-Dimethyl-6,7-diethoxy-tetrahydro-			p	Cl 50 69 IP		(90)

it was found to be dextrorotatory, it was called *d*-tubocurarine chloride. King (129, 130) showed that *d*-tubocurarine chloride and *l*-curine methochloride are isomeric, and proved by a series of Hofmann degradations that *d*-tubocurarine chloride has the following structure:

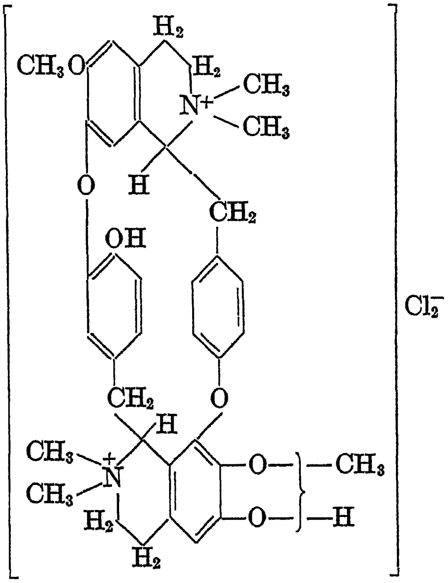
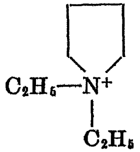
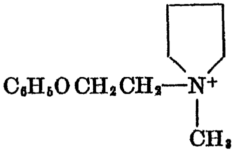
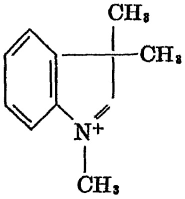


TABLE 13

Heterocyclic ammonium compounds

Miscellaneous compounds

QUATERNARY COMPOUND	STRUCTURE	PHARMACOLOGICAL ACTION					TOXIC DOSE	PARALYZING DOSE FROGS	REFERENCES
		Curariform action	Muscarinic action	Stimulating nicotinic action	Paralyzing nicotinic action	Other actions			
							mg./kg.	*mg./kg.*	
N,*N*-Diethylpyrrolidinium			—						(104)
N-Methyl-*N*-(β-phenoxyethyl)pyrrolidinium			—	++	⊕		Mice I M 140 SC		(106, 107, 178)
N,3,3-Trimethylindolinium							Rabbits Cl 200–500 SC		(211)

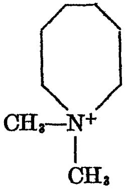
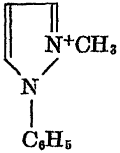
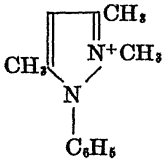
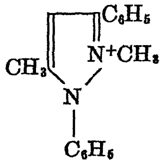
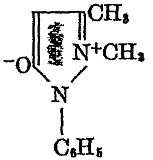
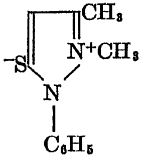
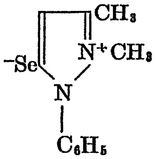
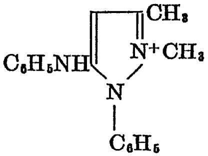
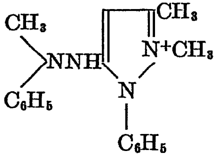
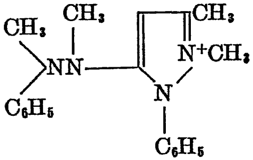
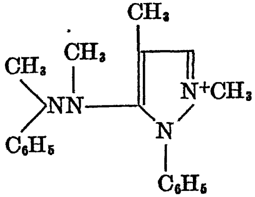
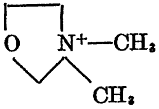
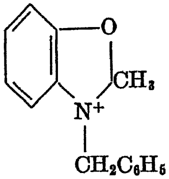
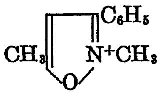
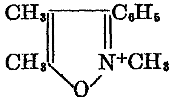
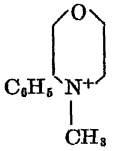
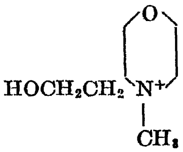
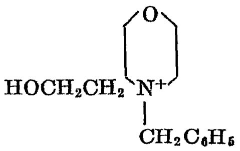
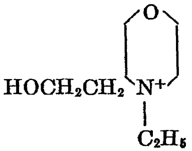
N,*N*-Dimethylhexahydro-azepinium			−	+	+		Mice Br M 23 SC		(104)
1-Phenyl-2-methylpyrazolium		⊕							(211)
1-Phenyl-2,3,5-trimethyl-pyrazolium		−				Central paralysis			(207, 211)
1,3-Diphenyl-2,5-dimethyl-pyrazolium		+				Central paralysis			(208)
Antipyrine		−	−	−	−				(134)

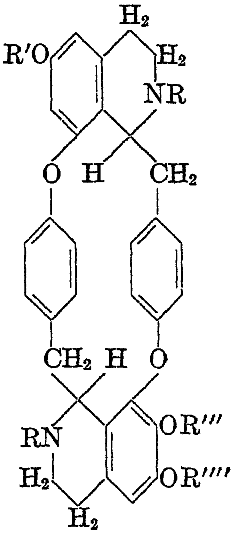
TABLE 13—*Continued*

QUATERNARY COMPOUND	STRUCTURE	PHARMACOLOGICAL ACTION					TOXIC DOSE	PARALYZING DOSE FROGS	REFERENCES
		Curariform action	Muscarinic action	Stimulating nicotinic action	Paralyzing nicotinic action	Other actions			
							mg./kg.	*mg./kg.*	
Thiopyrine						Central nervous poison			(208)
Selenopyrine						Central nervous poison			(134)
1-Phenyl-2,3-dimethyl-5-anilinopyrazolium						Stimulation followed by paralysis of central nervous system			(134)
1-Phenyl-2,3-dimethyl-5-(phenylmethylhydrazino)-pyrazolium		—				Central paralysis			(134)

1-Phenyl-2,3-dimethyl-5-(phenyldimethylhydrazino)pyrazolium		⊕							(134)
1-Phenyl-2,4-dimethyl-5-(phenyldimethylhydrazino)pyrazolium		⊕							(211)
N,N-Dimethyloxazolium			–	–	–				(30)
2-Methyl-3-benzylbenzoxazolium								300	(24)
2,5-Dimethyl-3-phenylisoxazolium		+				Central paralysis			(208)

QUATERNARY COMPOUND	STRUCTURE	PHARMACOLOGICAL ACTION					TOXIC DOSE	PARALYZING DOSE FROGS	REFERENCES
		Curariform action	Muscarinic action	Stimulating nicotinic action	Paralyzing nicotinic action	Other actions			
							mg./kg.	*mg./kg.*	
2,4,5-Trimethyl-3-phenylisoxazolium		⊕						Cl 200	(211)
N-Methyl-*N*-phenylmorpholinium								I 300	(24)
N-Methyl-*N*-(β-hydroxyethyl)morpholinium								I 300	(24)
N-Benzyl-*N*-(β-hydroxyethyl)morpholinium		+						I 300	(24)
N-Ethyl-*N*-(β-hydroxyethyl)morpholinium		+						I 300	(24)

King (128–133), Wintersteiner and Dutcher (223), and Dutcher (31) showed that various curare alkaloids have structures of the following two types:

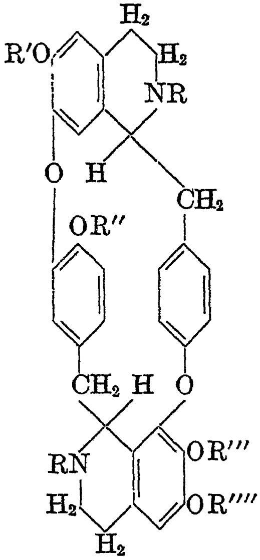


Type I

Protocuridine: R is CH_3; R′ or R⁗ or both are CH_3; R″ or R‴ or both are H (133)

Neoprotocuridine: R is CH_3; R′ and R⁗ are H; R″ and R‴ are CH_3 (132)

Isochondodendrine: R is CH_3; R′ or R⁗ or both are CH_3; R″ or R‴ or both are H (133)



Type II

l-Curine (*l*-bebeerine) and *d*-bebeerine: R is CH_3; R′ and R⁗ are CH_3; R″ and R‴ are H (131, 132)

d-Tubocurarine chloride: R is $(CH_3)_2$, making nitrogen quaternary; R′ is CH_3; R″ is H; one of R‴ and R⁗ is CH_3 and the other is H (129)

d-Chondocurine: R is CH_3; R′ is CH_3; R″ is H; R‴ and R⁗ are H and CH_3 in reverse of *d*-tubocurarine chloride (31)

d-Chondocurarine chloride: R is $(CH_3)_2$; R′, R″, R‴, and R⁗ are the same as in chondocurine (31)

Wieland and coworkers (217–220) have isolated a group of very active alkaloids from gourd or calabash curare, which they have named calabashcurarines and toxiferines. The different alkaloids are indicated by numerals placed after the names, such as calabashcurarine I, calabashcurarine II, etc. They were able to establish the empirical formulas for these alkaloids and to show that only one of the two nitrogens present is quaternary.

Karrer and coworkers (126, 127) recently published two papers describing preliminary work on structural determinations of these alkaloids. From titration data and preparation of an *N*-nitroso derivative they showed that the non-

TABLE 14

Alkaloids

Curare alkaloids

EMPIRICAL FORMULA	PHARMACOLOGICAL ACTION		TOXIC DOSES			PARALYZING DOSES					SAFETY INDEX RABBITS $\frac{\text{LD 50}}{\text{HDrD 50}}$	REFERENCES
	Curariform action	Other actions	Frogs	Mice	Rabbits	Frogs	Minutes to paralyze isolated nerve sartorius Millimoles/liter 1	0.1	Rabbit head-drop Units/mg.	HDrD 50		
			mg./kg.	*mg./kg.*	*mg./kg.*	*mg./kg.*	*minutes*			*mg./kg.*		
	++			$\underline{50}$ 4.4–6 SC $\underline{100}$ 7 SC	$\underline{50}$ 1.3 IV	2.5 –5 EL				0.6	47	(13, 19, 25, 87)
$C_{19}H_{26}N_2O$	++	Paralyzing nicotinic action	150	0.38–0.41 SC	0.34	Cl 0.2 –0.5 EL	3.7	7.0				(13, 86, 87, 117, 118, 210, 213, 216)
$C_{20}H_{23}N_2O$			0.13									(86)
$C_{22}H_{27}NO_4$	–	Central paralysis										(22, 139)
$C_{36}H_{38}N_2O_6$	+	Central depressant										(86, 216)
$(C_{38}H_{44}H_2O_6)^{++}I_2^-$	+++								5			(31)
$(C_{38}H_{44}N_2O_6)^{++}I_2^-$			20			20						(86, 129)
$(C_{40}H_{48}N_2O_6)^{++}I_2^-$	+++								18.3			(31)
$C_{36}H_{38}N_2O_6$	–	Central depressant										(69)
$(C_{38}H_{44}N_2O_6)^{++}I_2^-$	++								<0.4			(69, 223)
$(C_{40}H_{48}N_2O_6)^{++}I_2^-$	++								1.6			(69, 223)
$(C_{42}H_{52}N_2O_6)^{++}I_2^-$	⊕											(69)
$C_{36}H_{38}N_2O_6$	⊕											(223)
$(C_{38}H_{44}N_2O_6)^{++}Cl_2^-$	+++								19.75			(31, 223)
$C_{20}H_{23}NO_3$	+											(131)
$(C_{21}H_{26}NO_3)^+$	++		1.5		0.24							(13, 86, 131)
$C_{30}H_{38}N_2O_6$	+					HCl 45						(86, 131)
$(C_{38}H_{44}N_2O_6)^{++}Cl_2^-$	+++		0.5		1 SC	0.5			6.5			(13, 86, 129, 216, 223)
$(C_{40}H_{48}N_2O_6)^{++}Cl_2^-$	+++								60			(223)
$(C_{42}H_{52}N_2O_6)^{++}I_2^-$	++											(223)
$(C_{46}H_{60}N_2O_6)^{++}I_2^-$	–											(223)
$C_{20}H_{21}N_2^+$	+++					HCl 0.12–0.16 EL						(86, 217, 219)
$C_{20}H_{20}BrN_2^+$	+++					HCl 0.04 EL						(220)
$(C_{20}H_{20}N_3O_2)^+$	+++					HCl 0.008 EL						(220)

TABLE 14—*Concluded*

ALKALOID	EMPIRICAL FORMULA	PHARMACOLOGICAL ACTION		TOXIC DOSES			PARALYZING DOSES					SAFETY INDEX RABBITS $\frac{\text{LD 50}}{\text{HDrD 50}}$	REFERENC
		Curariform action	Other actions	Frogs	Mice	Rabbits	Frogs	Minutes to paralyze isolated nerve sartorius Millimoles/liter 1	 0.1	Rabbit head-drop Units/mg.	 HDrD 50		
				mg./kg.	*mg./kg.*	*mg./kg.*	*mg./kg.*	*minutes*			*mg./kg.*		
Calabashcurarine III	$C_{20}H_{21}N_2^+$	–											(220)
Toxiferine I	$C_{20}H_{21}N_2^+$	+++					0.23–0.6 EL						(217, 218)
Calabashcurarine II	$C_{20}H_{23}N_2^+$	++					HCl 2–4 EL						(86, 217, 219)
Bromocalabashcurarine II	$C_{20}H_{22}BrN_2^+$	+++					0.6 EL						(220)
Nitrocalabashcurarine II	$(C_{20}H_{22}N_3O_2)^+$	++					8 EL						(220)
Calabashdihydrotoxiferine I	$C_{20}H_{23}N_2^+$	+++					0.06 EL						(217)
Calabashisodihydrotoxiferine I	$C_{20}H_{23}N_2^+$	+++					0.12–0.16 EL						(217)
Toxiferine II	$C_{20}H_{23}N_2^+$	+++					0.2 EL						(217)
Toxiferine IIa	$C_{20}H_{23}N_2^+$	+++					0.8–1.2 EL						(217)
Toxiferine IIb	$C_{20}H_{23}N_2^+$	++					4–6 EL						(217)
Calabashtoxiferine II	$C_{20}H_{23}N_2^+$	+++					0.4 EL						(217)

quaternary nitrogen was secondary and not basic. Heating the quaternary chloride gave them methyl chloride and a tertiary base, a result which indicated that there was a methyl group on the quaternary nitrogen. They interpreted titration data on the tertiary base as indicating that the tertiary nitrogen is in a reduced isoquinoline ring system and is common to two rings.

Freise (67) and Carneiro (22) have isolated alkaloids from various South American plants believed to be associated with curare: eucurarine from *Strychnos spp.*, macowbeine from *Macoubea guyanensis*, and lethaline and curalethaline from *Strychnos lethalis*. No information was found about their physiological action or chemical nature.

The active constituents of curare preparations are quaternary alkaloids; the tertiary alkaloids have a very weak or no paralyzing action, but become very effective on conversion to the quaternary bases. *d*-Tubocurarine chloride is the active ingredient of the curare preparations which have been most widely used and has a paralyzing action on frogs from five to ten times that of standard ampuled curare. Chondocurine, which is a tertiary alkaloid, has only a weak curariform action; however, when it is converted to the dimethochloride, it has an effectiveness about three times that of *d*-tubocurarine chloride. Wintersteiner and Dutcher (223) stated that this is the first instance in which a tertiary alkaloid of this type has been converted to a quaternary base which approximates or exceeds in potency the naturally occurring active constituents of curare.

When the two free hydroxyl groups of *d*-tubocurarine chloride are methylated, the resulting compound has a paralyzing action much greater than that of the original compound. Ethylation does not show this marked effect, and butylation abolishes the activity completely (223).

The effectiveness of some of the calabashcurarines is greater than that of *d*-tubocurarine. Calabashcurarine I paralyzes frogs in doses of 0.12–0.16 mg./kg. as compared to a dose of 0.5 mg./kg. for *d*-tubocurarine chloride. Calabashcurarine I can be readily converted to monobromo or mononitro derivatives which paralyze frogs in doses of 0.04 and 0.008 mg./kg., respectively. These are extremely low paralyzing doses.

The effective paralyzing action of the curare preparations, as was stated in the introduction, led to early clinical investigations for treatment of various muscle spasms and for relaxation of muscles during surgical operations (7, 17, 20, 23, 29, 70, 74, 77, 80, 147, 186), with promising results in some cases. The fact that the composition of various curare preparations was not uniform has caused unreproducible results in clinical applications. Three things that would be desirable in a drug of this type are (*1*) a powerful and prolonged paralyzing action, (*2*) a relatively large margin of safety, and (*3*) effectiveness when given orally. Intocostrin, which is a standardized, purified curare preparation, has the powerful and prolonged action desired but is ineffective orally and has a relatively small margin of safety.

Cohnberg (27) reported recently that intocostrin and *d*-tubocurarine chloride have an effect on the central nervous system. The action is one of stimulation of the central nervous system so that hyperexcitability and clonic convulsions are produced. Signs of stimulation are more conspicuous in some animals than others. Central nervous depressants such as sodium amytal or cyclopropane decrease or prevent intocostrin convulsions, but artificial respiration has little effect in controlling convulsions. This central stimulation is another disadvantage of curare.

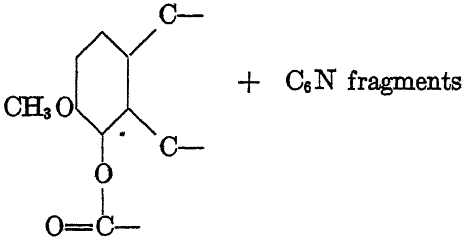
Clinically, standardized curare preparations in doses of 25 mg. given intravenously and 10–40 mg. given intramuscularly have an effect lasting 1 to 2 days, so that injections are given about three times a week. Patients still show some signs of curare paralysis up to 12 days after administration. The paralyzing effect occurs immediately after intravenous injection and in 20 to 30 min. after intramuscular injection (19).

2. Erythrina alkaloids (table 15)

The extracts of seeds of plants of the *Erythrina* species have been known for many years to exhibit a paralyzing action in animals. Only recently, however, has their paralyzing action been shown to be curare-like (213).

Folkers and Major (57) isolated an active alkaloid erythroidine from *Erythrina americana* Mill., and found that it consisted of at least two isomeric dextrorotatory alkaloids, which were designated as α- and β-erythroidine. Since the β-form is more readily obtained in pure state, it has been investigated chemically and physiologically to the greater extent. In further examination of various *Erythrina* species, some twelve different alkaloids, most of which show curare-like paralysis, have been isolated (40, 43–48, 54–57, 61, 63–65). A series of patents have been issued to Folkers and coworkers on procedures for isolating and purifying these various alkaloids (41–42, 49–53, 58–60, 62).

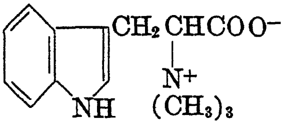
β-Erythroidine has been shown to have the empirical formula $C_{16}H_{19}NO_3$ and to contain a tertiary nitrogen common to two rings, a methoxyl group, two olefinic double bonds, and a lactone ring. It was shown to contain an indole nucleus by isolation of indole from a potassium hydroxide fusion. After demethylation, hydrolysis, methylation, and oxidation of β-erythroidine, 3-methoxyphthalic anhydride was obtained. After dehydrogenation, hydrolysis, methylation, and oxidation, hemipinic anhydride (3,4-dimethoxyphthalic anhydride) was obtained. These facts would indicate that a partial structure for β-erythroidine might be as follows:



It is highly probable that the ring system of erythroidine differs from that of the other erythrina alkaloids (52, 213).

By catalytic hydrogenation β-erythroidine is converted into dihydro-β-erythroidine and two tetrahydro isomers, which are called α-tetrahydro-β-erythroidine and β-tetrahydro-β-erythroidine (52, 58, 213).

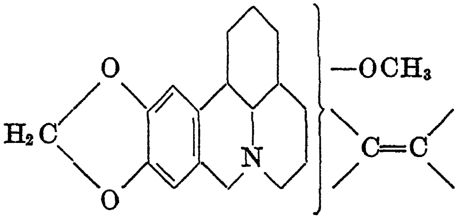
One of the compounds isolated from *Erythrina* extracts was called hypaphorine. It was shown to be the betaine of tryptophan (44).



Hypaphorine

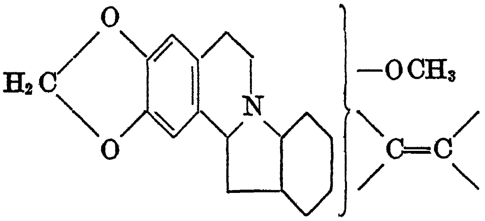
Hypaphorine does not possess curare activity, but the methyl ester does. This is in line with observations of other betaine-type compounds.

Of the other alkaloids isolated from *Erythrina* species, the first structural investigation was carried out on erythramine ($C_{18}H_{21}NO_3$), which was shown to have a tertiary nitrogen common to two rings, a methoxyl group, one olefinic double bond, and five fused rings, one of which was aromatic (45). Because of the close similarity of the ultravioletabsorption curves of dihydroerythramine and 6,7-methylenedioxy-1,2,3,4-tetrahydroisoquinoline, the following structure was proposed (47):



It was pointed out, however, that one ring might be five-membered.

In later degradation studies, indole was isolated from potassium hydroxide fusions (55). Interpretation of the indole formation suggested that erythramine might be one of the following:



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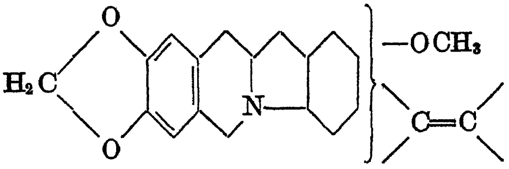


II

TABLE 15

Alkaloids

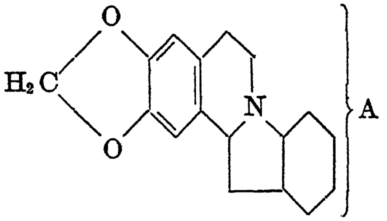
Erythrina alkaloids

ALKALOID	EMPIRICAL FORMULA	CURARIFORM ACTION	OTHER ACTIONS	TOXIC DOSES			PARALYZING DOSES		SAFETY INDEX FOR RABBITS LD 50 / HDrD 50	REFERENCES
				Mice	Rats	Miscellaneous	Frogs	Rabbit head-drop HDrD 50		
				mg./kg.	*mg./kg.*	*mg./kg.*	*mg./kg.*	*mg./kg.*		
Hypaphorine... (Tryptophan betaine)	$C_{14}H_{17}N_2O_2$	–								(44)
Hypaphorine methyl ester	$(C_{15}H_{20}N_2O_2)^+$	⊕		I 50 450			I 100 EL			(44)
β-Erythroidine.	$C_{10}H_{19}NO_3$	++	Muscarinic	HCl 50 45 SC HCl 100 50 SC HCl 50 120 OS HCl 100 140 OS Na⁺ 50 230 SC	HCl 50 1260 SC HCl 50 510 OS HCl 50 39.9 IV	Rabbits HCl M 5 HCl 50 8.6 IV Dogs HCl M < 3.5 HCl 50 8.8 IV	HCl 3-8 EL Na⁺ 75 EL	7.6	88%	(20, 24, 25, 26, 57, 231)
β-Erythroidine methiodide.	$(C_{17}H_{22}NO_3)^+I^-$	+					I 200 EL			(213)
Dihydro-β-erythroidine	$C_{16}H_{21}NO_3$	++		HCl 50 9.3 SC HCl 50 7.5 OS	HCl 230 SC HCl 320 OS HCl 8.9 IV	Rabbits HBr M 1 HBr 50 2.1 IV Dogs HBr M 1 HBr 50 1.1 IV	HCl 0.6 EL Na⁺ 0.5 EL	1.5	73%	(24, 25, 26, 52, 213)
α-Tetrahydro-β-erythroidine..	$C_{16}H_{23}NO_3$	+					HBr 200 EL			(213)

β-Tetrahydro-β-erythroidine	$C_{16}H_{23}NO_3$	++		HBr 50 9.5 SC			HBr 0.5 EL			(213)
Erysopine....	$C_{17}H_{19}NO_3$	++		HCl 50 15 SC HCl 50 18 OS			HCl 4 EL			(48, 56, 212)
Tetrahydroerysopine......	$C_{17}H_{23}NO_3$	+					HBr 40 EL			(212)
Erysonine....	$C_{17}H_{19}NO_3$	+					HCl 100 EL			(48, 63)
Erythraline .	$C_{18}H_{19}NO_3$	++		HBr 50 72 SC HBr 50 80 OS			HBr 10 EL			(212, 213)
Erythraline methiodide..	$(C_{19}H_{22}NO_3)^+I^-$	+					I 100 EL I 50 EL			(55, 212)
Dihydroerythraline......	$C_{18}H_{21}NO_3$	+		HBr 300			HBr 300 EL			(55)
Erythramine..	$C_{18}H_{21}NO_3$	++					HBr 10 EL			(44, 46)
Erythramine methiodide.	$(C_{19}H_{24}NO_3)^+I^-$	++					I 40 EL			(55, 219)
Dihydroerythramine......	$C_{18}H_{23}NO_3$	+		HBr 50 104 SC			HBr 300 EL			(45, 212)
Erythratine..	$C_{18}H_{21}NO_4$	+					HBr 75 EL			(46)
Erythratine methiodide..	$(C_{19}H_{24}NO_4)^+I^-$						I 300 EL			(212)
Dihydroerythratine	$C_{18}H_{23}NO_4$						HBr 100 EL			(212)
Erysodine.....	$C_{18}H_{21}NO_3$			HCl 50 100 SC HCl 50 155 OS			HCl 10–15 EL			(48, 56, 212)
Tetrahydro-erysodine....	$C_{18}H_{25}NO_3$						HBr > 300 EL			(219)
Erysovine.....	$C_{18}H_{21}NO_3$	++					HCl 3 EL Na^+ 3 EL			(48, 56, 212)
Erysocine.....	$C_{18}H_{21}NO_3$	++								(48)
Erysothiopine..	$C_{19}H_{21}NO_7S$	++		Na^+ 50 76 SC			Na^+ 1 EL			(56, 212)
Erysothiovine..	$C_{20}H_{23}NO_7S$	++					Na^+ 1 EL			(56)

Structure I was favored over II because of biogenetical relationships, that is, I is a 1-benzyltetrahydroisoquinoline derivative, many of which occur naturally.

Erythramine, erythraline, and erythratine were shown to have carbon skeletons containing five fused rings, four of which were identical for all three of the alkaloids. The fifth ring differed in unsaturation and substitution (55). The following structures were proposed for these three alkaloids:



Erythramine: A = CH_3O— and one double bond
Erythraline: A = CH_3O— and two double bonds
Erythratine: A = CH_3O—, HO—, and one double bond

The alkaloids isolated from various *Erythrina* species are of two types: those occurring as free alkaloids, and those which must be liberated by hydrolysis. The stem *erythr-* has been used in naming the first group, while the stem *eryso-* has been used for the liberated alkaloids (48). Thus, erysodine, erysopine, and erysonine were isolated after hydrolysis of extracts with hydrochloric acid. Erysodine, erysopine, and erysovine have identical nuclear structures, as the complete methylation of the alkaloids produces identical compounds (54). By chromatographic purification, erysocine, which was thought to be a single alkaloid, was shown to be a mixture of erysodine and erysovine, possibly a molecular complex (61). Since these liberated alkaloids contain a phenolic hydroxyl group and the free alkaloids do not, it was believed that the liberated alkaloids were tied up through this group (56). No indication has been given as to whether these "eryso-" alkaloids have the same general ring system as erythramine, erythradine, and erythratine. The substituents found for these alkaloids are as follows: erysopine has one $—OCH_3$, one alcoholic —OH, and one phenolic —OH; erysodine has two $—OCH_3$ groups and one phenolic —OH; and erysovine has two $—OCH_3$ groups and one phenolic —OH (48).

Folkers, Koniuszy, and Shavel (56) isolated two sulfur-containing alkaloids, erysothiovine and erysothiopine, which were found to give erysovine and erysopine on acid hydrolysis. The other compound formed in the hydrolysis was found to be sulfoacetic acid. Since the sulfur-containing alkaloids were weakly basic, the sulfoacetic acid residue was believed to be attached as a sulfonic ester to the phenolic hydroxyl group.

The erythrina alkaloids are the first compounds containing a tertiary nitrogen that exhibit a pronounced curariform action. In all other cases, the conversion of a tertiary base which has a curare action to a quaternary compound greatly enhances the action. This is not the case with the erythrina alkaloids, as β-erythroidine is reduced in effectiveness by a factor of about twenty on conversion to the methiodide. This is also true to a lesser extent with erythraline, erythramine, and erythratine.

β-Erythroidine paralyzes frogs in doses of 3–8 mg./kg. as compared to doses of 0.5 mg./kg. of *d*-tubocurarine chloride. Dihydro-β-erythroidine is five to ten times more effective than β-erythroidine itself. The β-tetrahydro-β-erythroidine also has an action greater than that of the unsaturated alkaloid, but the α-isomer is very much less effective.

Erysothiopine and erysothiovine are three to four times as effective as erysopine and erysovine, and differ from them only by the presence of a sulfoacetic residue on the ring. This indicates that the sulfoacetic group, attached as a sulfonic ester, enhances curare activity.

Because of the effectiveness of β-erythroidine and dihydro-β-erythroidine and particularly because they are effective orally, they have been investigated clinically with some success as possible curare substitutes (17, 19, 28, 33, 37, 70, 71, 72, 73, 77, 79, 81, 82, 148, 184, 185, 221, 222). The paralyzing action of β-erythroidine is not as intense or prolonged as that of standardized curare preparations, but it has a greater margin of safety. β-Erythroidine given intravenously has an effect lasting at most 24 hr., making it necessary to give injections daily. Burman (20) reported that it has a hypnotic effect when given orally that is not shown when given by injection.

3. Quaternary derivatives of cinchona alkaloids (table 16)

Quaternary salts of quinine and cinchonine have been prepared and are found to possess marked curare activity. The nitrogen of the quinuclidine ring is the most basic and is in the quaternary form in the monoalkylquininium salts. The diquaternary salts have only about half the curare activity of the monoalkylquininium salts.

In the series of monoalkylquinium salts, a maximum effectiveness is shown by the amyl derivative in paralysis of both frogs and rabbits. If the ratio of the dose in the rabbit head-drop test to the toxic dose for a rabbit is taken as an indication of margin of safety, the amylquininium salt is the safest to use. The amylquininium salt is about one-sixth as effective in frogs or rabbits as standardized curare; compared to β-erythroidine, it is less effective in frogs but more effective in rabbits. Using the above ratio as the margin of safety, the quininium salt is safer than either curare or β-erythroidine.

The quininium salts have an action of about one-third the duration of that of curare (25). Harvey (78) found that quinine itself has a weak curare action which is greatly increased by formation of the monoquaternary salt, the central and other effects being greatly reduced or abolished. He found that methylquininium chloride is effective orally, a dose of 150–200 mg. producing in cats a sequence of events similar to those caused by curare injected into humans.

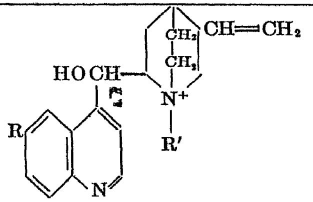
Methylcinchoninium sulfate has about the same action as the corresponding quininium salt; however, the amylcinchoninium salt is less effective than the corresponding quininium salt.

Quinine methochloride and ethochloride have been investigated clinically as

TABLE 16

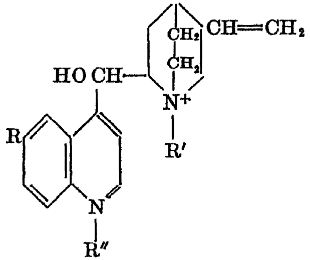
Alkaloids

Quaternary derivatives of cinchona alkaloids

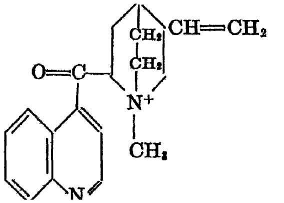


QUATERNARY ALKALOID	R	R′	PHARMACOLOGICAL ACTION: Curariform action	PHARMACOLOGICAL ACTION: Other actions	TOXIC DOSES: Rabbits	TOXIC DOSES: Dogs	TOXIC DOSES: Rats	PARALYZING DOSES: Frogs	PARALYZING DOSES: Rabbits	PARALYZING DOSES: Rabbit head-drop HDrD 50	SAFETY INDEX RABBITS LD 50 / HDrD 50	REFERENCES
					mg./kg.	*mg./kg.*	*mg./kg.*	*mg./kg.*	*mg./kg.*	*mg./kg.*		
N-Methylquininium	—OCH$_3$	—CH$_3$	++		Cl 50 7 IV	Cl M 15 IV Cl 50 16.3 IV	Cl M <5 IV Cl 50 5 IV	Cl 40 EL Br 50 I 60	Cl 7.5 Br 5	Cl 5	72	(24, 25, 26, 78, 211)
N-Ethylquininium	—OCH$_3$	—C$_2$H$_5$	++		Cl 50 7.6 IV	Cl 50 12.9 IV Cl M 8.5 IV	Cl 50 5.2 IV Cl M <5 IV	Cl 30 EL	Cl 5	Cl 3.3	44	(25, 26)
N-Propylquininium	—OCH$_3$	—C$_3$H$_7$	++		Br 50 3.4 IV Cl 50 2.9 IV	Br 50 5.9 IV Cl 50 4.3 IV	Br 50 4.2 IV Cl 50 6.9 IV	Br 50 EL Cl 70 EL		Br 3.2 Cl 2.4	Br 93 Cl 81	(25)
N-Isopropylquininium	—OCH$_3$	—C$_3$H$_7$(iso)	+		Cl 50 13.2 IV	Cl 50 9.3 IV	Cl 50 20.8 IV	Cl 200 EL		Cl 8.6	65	(25)
N-Butylquininium	—OCH$_3$	—C$_4$H$_9$	++		Cl 50 9.5 IV	Cl 50 5.8 IV	Cl 50 7.2 IV	Cl 50 EL		Cl 4.2	44	(25)
N-Amylquininium	—OCH$_3$	—C$_5$H$_{11}$	++		Br 50 10 IV	Br 50 15.6 IV	Br 50 4.5 IV	Br 30 EL		Br 3.9	39	(25)
N-Isoamylquininium	—OCH$_3$	—C$_5$H$_{11}$(iso)	++		Cl 50 10.3 IV	Cl 50 20 IV	Cl 50 5.3 IV	Cl 70 EL		Cl 4.3	41	(25)

N-Hexylquininium..........	—OCH_3	—C_6H_{13}		+		Br $\underline{50}$ 10 IV	Br $\underline{50}$ 20.8 IV	Br $\underline{50}$ 9.3 IV	Br 80 EL		Br 4.1	41	(25)
N-Methylcinchoninium	—H	—CH_3		++					SO_4 26–40				(32, 87)
N-Amylcinchoninium...	—H	—C_5H_{11}		++					I 50–80				(32, 87)
N-Carbomethoxymethylcinchoninium	—H	—CH_2COOCH_3		++					I 50				(87)



	R	R′	R″										
N,*N*-Dimethylquininium	—OCH_3	—CH_3	—CH_3	+					I 150				(24, 211)
N,*N*-Dimethylcinchoninium... .	—H	—CH_3	—CH_3	⊕									(211)
N-Methylcinchonicinium....................				⊕	Convulsant								(211)



curare substitutes (8, 79, 81). The results were described as "adequate" in the treatment of spastic paralysis and in shock therapy; the margin of safety, however, is uncertain.

4. Quaternary derivatives of pyridine alkaloids (table 17)

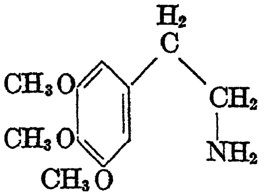
Various alkylconiinium, alkylconhydrinium, and alkylnicotinium salts possess curare actions. The most effective salt reported, ethylbenzylconiinium iodide, has a paralyzing action in frogs about one-fiftieth of that of curare or about the same as that of methylquininium iodide.

The presence of two different alkyl groups on the nitrogen of coniine and conhydrine gives rise to two stereoisomers, since the quaternary nitrogen and the adjacent carbon are now asymmetric. The higher-melting or β-isomer is always more effective than the lower-melting or α-isomer. In the benzylalkylconiinium series through the benzylbutyl derivative, the effectiveness decreases with increasing length of the alkyl group. However, the isoamylbenzyl derivative has an action comparable to that of the ethylbenzyl derivative. In general, the conhydrinium salts are less effective than the coniinium.

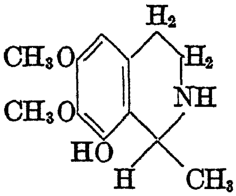
The nicotinium salts have only a weak curare action. *N*,*N*′-Diethylnicotinium iodide is about one-third as effective as *N*-ethylnicotinium iodide. This observation is in line with results in the quininium series, where conversion of both nitrogens to the quaternary form reduced the intensity of the curare action. It is interesting to note that a quaternary nitrogen in a saturated ring system caused marked curare action, which is reduced when a nitrogen in an unsaturated ring in the same molecule is converted to a quaternary nitrogen.

5. Isoquinoline alkaloids (table 18)

The simple isoquinolinium compounds were discussed on page 351. In that discussion, mention was made of the similarity in physiological action of the isoquinolines and β-arylethylamines. This is also borne out by the similarity of action of mescaline and the cactus alkaloid, anhalonidine.



Mescaline



Anhalonidine

Both have a depressant action on the central nervous system. Anhalonidine is reported to have a curariform action in large doses (86).

Laidlaw (138) reported that isoquinoline derivatives substituted in the 6-, 7-, and 8-positions with methoxy and methylenedioxy groups are convulsant when the nitrogen is tertiary, but devoid of this effect when the nitrogen is quaternary. Pyman (159) made these same observations with 6,7-dimethoxy derivatives; no mention was made in either case of peripheral paralyzing actions.

Macht (142) found that papaverine and related alkaloids tend to inhibit contractions and to relax the tonus of smooth muscle. The inhibitory or depressor effect seems to reside in the benzyl portion of the molecule. Papaverine, narcotine, hydrastine, and hydrastinine exhibit this depressor effect, but isoquinolines which do not have the 1-benzyl group do not have this relaxing effect and may cause contractions.

Pohl (157) reported that papaverinium salts have no curare action, but give a central paralysis. However, Takase (204) reported that papaverinium salts paralyze motor nerve endings. In this case, the nitrogen is present in an unsaturated ring.

Coclaurine, which has the nitrogen present in a saturated ring, has a weak curare action (156) although it is only a secondary base. No information on the quaternary salt could be found, but in view of previous results, it should have a marked curare action.

The alkylation of canadine leads to two stereoisomers, and again the higher-melting or β-isomer is more effective (ten times) than the α-isomer. β-*l*-Canadine methochloride paralyzes frogs in a dose of 2.5 mg./kg., an effect which is comparable to that of standardized curare. This compound is particularly interesting, since it contains a quaternary nitrogen which is common to two rings.

On the other hand, palmatine paralyzes the central nervous system and the respiratory center. This is also true of columbamine and jatrorrhizine, which are isomers and differ only from palmatine in that one methoxy group is replaced by hydroxyl (11, 86). These compounds also contain a quaternary nitrogen common to two rings, but one ring is unsaturated.

The quaternary salts of some of the morphine alkaloids are reported to have curare activity; the intensity of their action, however, is not great enough to make them of interest.

6. Quaternary derivatives of miscellaneous alkaloids (table 19)

Quaternary salts of some of the tropine alkaloids possess curare activity. Benzyl- and methyl-atropinium bromides paralyze frogs in doses almost equivalent to that of β-erythroidine. The only example found where there is any significant difference in the effectiveness of different salts of the same onium ion is that of benzylatropinium bromide and iodide. The bromide is reported to be sixty times as effective as the iodide, an observation that seems doubtful.

Quaternary salts of some of the indole alkaloids possess curare activity. Of the strychninium and brucinium salts reported, the benzyl derivatives are the most effective, benzylstrychninium bromide being comparable to β-erythroidine in paralyzing frogs.

Quaternary salts of two alkaloids of indefinite structure, dendrobine and veratrine, have been reported but have little curare activity.

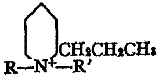
E. α-GLYCEROL ETHERS (TABLE 20)

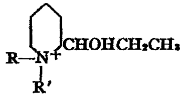
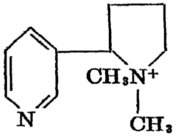
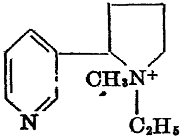
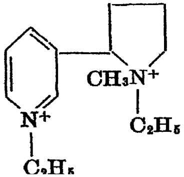
Most of the 143 compounds of this type which were investigated by Berger and Bradley (9) give paralysis only in doses which are lethal to some of the

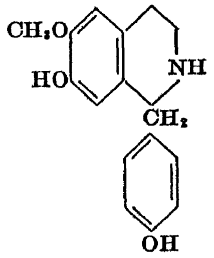
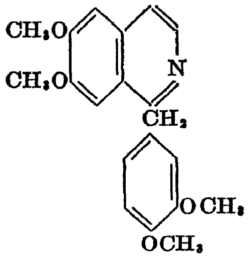
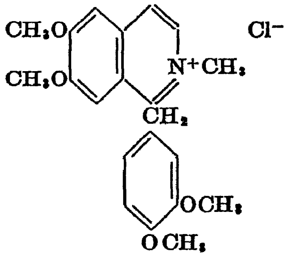
TABLE 17

Alkaloids

Quaternary derivatives of pyridine alkaloids

CONIINIUM COMPOUND			CURARIFORM ACTION	TOXIC DOSE	PARALYZING DOSE FROGS	REFERENCES
	R	R′				
				mg./kg.	mg./kg.	
N,*N*-Dimethyl	$—CH_3$	$—CH_3$	+	Mice I 30–60	I 60	(117,211)
N-Benzyl-*N*-ethyl- (β-Isomer)	$—CH_2C_6H_5$	$—C_2H_5$	++		I 25	(87,211)
N-Benzyl-*N*-ethyl- (α-Isomer)	$—CH_2C_6H_5$	$—C_2H_5$	++		I 43	(87)
N-Benzyl-*N*-propyl- (β-Isomer)	$—CH_2C_6H_5$	$—C_3H_7$	+		I 64	(87,211)
N-Benzyl-*N*-propyl- (α-Isomer)	$—CH_2C_6H_5$	$—C_3H_7$	+		I 77	(87)
N-Benzyl-*N*-butyl- (β-Isomer)	$—CH_2C_6H_5$	$—C_4H_9$	+		I 107	(87,211)
N-Benzyl-*N*-butyl- (α-Isomer)	$—CH_2C_6H_5$	$—C_4H_9$	+		I 120	(87)
N-Benzyl-*N*-isoamyl- (β-Isomer)	$—CH_2C_6H_5$	$—C_5H_{11}$(iso)	++		I 33	(87,211)
N-Benzyl-*N*-isoamyl- (α-Isomer)	$—CH_2C_6H_5$	$—C_5H_{11}$(iso)	++		I 42	(87)
N-Allyl-*N*-ethyl- (β-Isomer)	$—CH_2CH{=}CH_2$	$—C_2H_5$	++		I 45	(87)
N-Allyl-*N*-ethyl- (α-Isomer)	$—CH_2CH{=}CH_2$	$—C_2H_5$	++		I 52	(87)

CONHYDRINIUM COMPOUND							
	R	R′					
N-Benzyl-*N*-ethyl-................ (β-Isomer)	$—CH_2C_6H_5$	$—C_2H_5$	+		I	59	(87)
N-Benzyl-*N*-ethyl-.... .... (α-Isomer)	$—CH_2C_6H_5$	$—C_2H_5$	+		I	65	(87)
N-Benzyl-*N*-propyl-............... (β-Isomer)	$—CH_2C_6H_5$	$—C_3H_7$	+		I	67	(87)
N-Benzyl-*N*-propyl-............... (α-Isomer)	$—CH_2C_6H_5$	$—C_3H_7$	+		I	80	(87)
N-Benzyl-*N*-isoamyl-.............. (β-Isomer)	$—CH_2C_6H_5$	$—C_5H_{11}$(iso)	+		I	72	(87)
N-Benzyl-*N*-isoamyl-.............. (α-Isomer)	$—CH_2C_6H_5$	$—C_5H_{11}$(iso)	+		I	86	(87)
NICOTINIUM COMPOUND	STRUCTURE						
N-Methyl-.........................			+	Rabbits I 800–1200 SC	I SO_4	180 1000–1670	(32,87,211)
N-Ethyl-..........................			+		I SO_4	150–250 200–333	(32,87,211)
N,*N*′-Diethyl-.....................			+		I	500	(87,211)

ALKALOID	STRUCTURE OR TYPE	PHARMACOLOGICAL ACTION		TOXIC DOSE	PARALYZING DOSE FROGS	REFERENCES
		Curari-form action	Other actions			
				mg./kg.	*mg./kg.*	
Coclaurine		+				(129)
Papaverine		–	Central paralysis			(142, 157)
Papaverine methochloride		?	Central paralysis			(117, 157, 204)

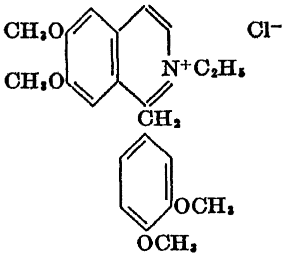
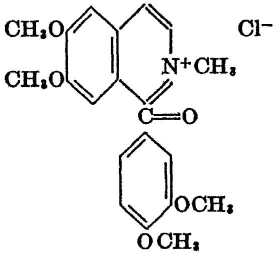
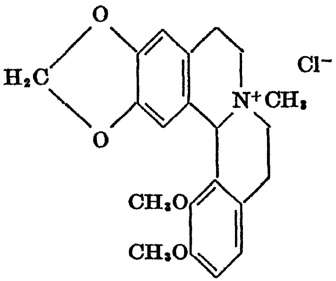
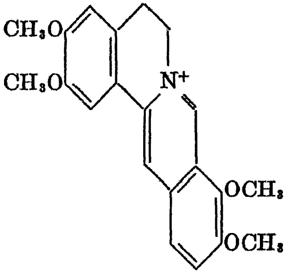
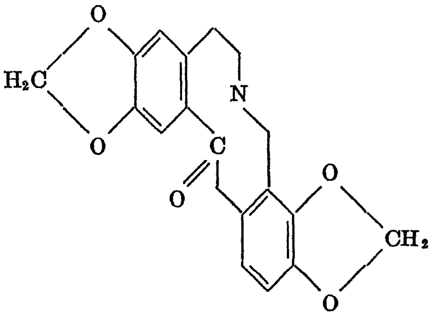
Papaverine ethochloride		?	Central paralysis			(157, 211)
Papaveraldine methochloride		?	Central paralysis			(117, 157)
α-*l*-Canadine methochloride		++			Cl 25	(137, 211)
β-*d*-Canadine methochloride		⊕				(137)
α-*l*-Canadine methochloride		++			Cl 2.5	(137, 211)
β-*d*-Canadine methochloride		⊕				(137)

TABLE 18—*Continued*

ALKALOID	STRUCTURE OR TYPE	PHARMACOLOGICAL ACTION		TOXIC DOSE	PARALYZING DOSE FROGS	REFERENCES
		Curariform action	Other actions			
				mg./kg.	*mg./kg.*	
Palmatine			Central paralysis			(11, 86)
Protopine		⊕				(86)
Tetrandrine methiodide	$(C_{39}H_{45}N_2O_6)^+I^-$ (Bisbenzylisoquinoline type)		Muscarinic and nicotinic actions			(140)

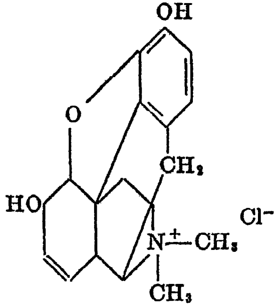
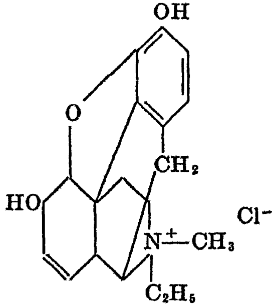
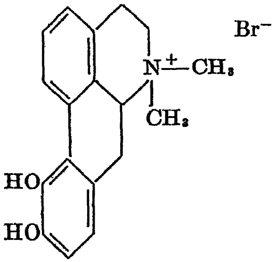
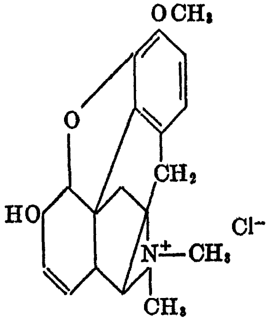
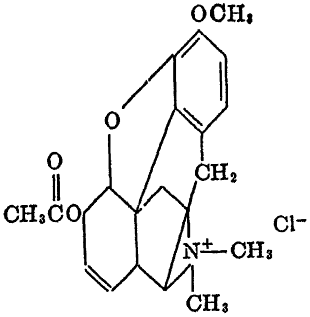
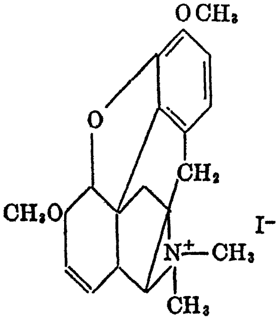
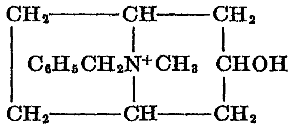
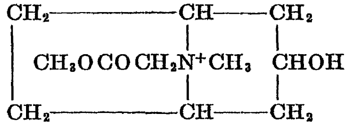
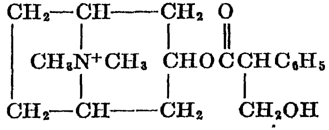
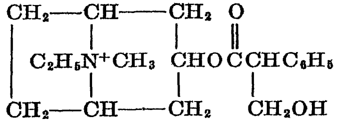
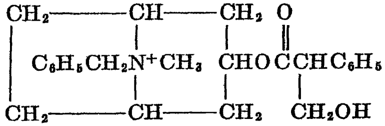
Morphine methochloride`		⊕		Mice Cl 7.5–10 SC	Cl 167	(117, 122, 211)
Morphine ethochloride		⊕				(211)
Apomorphine methobromide		⊕			Br 100	(211)

TABLE 18—*Concluded*

ALKALOID	STRUCTURE OR TYPE	PHARMACOLOGICAL ACTION		TOXIC DOSE	PARALYZING DOSE FROGS	REFERENCES
		Curari-form action	Other actions			
				mg./kg.	*mg./kg.*	
Codeine methochloride		⊕		Mice Cl 17 SC Br 30 SC		(117, 122, 211)
Acetylcodeine methochloride				Mice Cl 9 SC		(211)

Thebaine methiodide		⊕		Rabbits I 200	SO_4 200	(117,122, 211)

QUATERNARY ALKALOID	STRUCTURE OR EMPIRICAL FORMULA	PHARMACOLOGICAL ACTION		TOXIC DOSE	PARALYZING DOSES			REFERENCES
		Curari-form action	Other actions		Frogs	Minutes to paralyze isolated nerve sartorius		
						Millimoles/liter 1	10	
				mg./kg.	mg./kg.	minutes		
N-Benzyltropinium.		+			I 1000			(87)
N-Carbomethoxymethyltropinium..... ...		+			I 1670			(87)
N-Methylatropinium....		++		Rabbits I 180 SC SO_4 150 SC	Br 6–10			(32,87,117, 211)
N-Ethylatropinium		+						(211)
N-Benzylatropinium..		++			Br 10–16 I 600			(32,87,211)

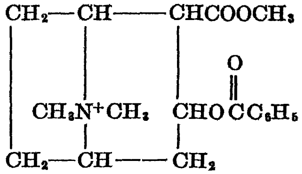
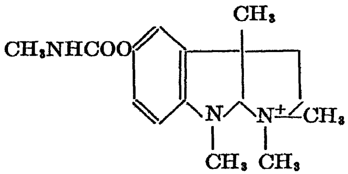
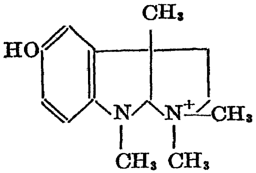
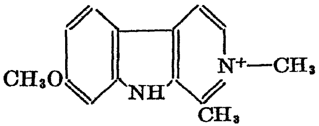
N-Methylcocainium.........		⊕						(211)
N-Methylphysostigminium...... (*N*-Methyleserinium)			Marked miotic; central depressant	Mice I 80 0.75–1 IV I 80 250–300 OS				(3, 201, 202)
N-Methyleserolinium		⊕						(201)
N-Methylharminium............			Weak nicotinic					(140)
N-Methylisocalycanthinium......	$(C_{13}H_{17}N_2)^+$ Indole type	+	Convulsant; respiratory paralysant		50–100			(86, 151, 211)

TABLE 19—*Concluded*

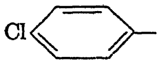
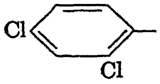
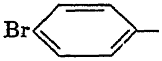
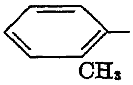
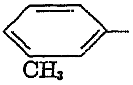
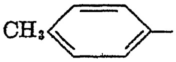
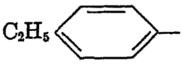
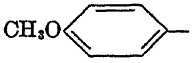
QUATERNARY ALKALOID	STRUCTURE OR EMPIRICAL FORMULA	PHARMACOLOGICAL ACTION		TOXIC DOSE	PARALYZING DOSES			REFERENCES
		Curariform action	Other actions		Frogs	Minutes to paralyze isolated nerve sartorius: Millimoles/liter 1	Minutes to paralyze isolated nerve sartorius: Millimoles/liter 10	
				mg./kg.	*mg./kg.*	*minutes*		
N-Methylstrychnium	$(C_{22}H_{25}N_2O_2)^+$ Indole type	++		Mice Cl 5 SC	SO_4 8–13	I 3–3.6	6.3	(32, 87, 117, 118, 121, 122, 211)
N-Ethylstrychnium	$(C_{23}H_{27}N_2O_2)^+$	++			SO_4 25–40	I 5.5		(32, 87, 121, 211)
N-(β-Hydroxyethyl)strychnium	$(C_{23}H_{27}N_2O_3)^+$	++			Cl 16–23			(211)
N-Benzylstrychninium	$(C_{28}H_{29}N_2O_2)^+$	++			Br 6–10			(32, 87)
N-Carbomethoxymethylstrychnium	$(C_{24}H_{27}N_2O_4)^+$	++			I 25			(87)
N-Methylbrucinium	$(C_{24}H_{29}N_2O_4)^+$ Indole type	+			Br 60 I 25–70			(24, 32, 87, 117, 122)

N-Ethylbrucinium..........	$(C_{25}H_{31}N_2O_4)^+$	++			SO_4 25–40			(32, 87, 211)
N-Benzylbrucinium..........	$(C_{30}H_{33}N_2O_4)^+$	++			Br 15–25			(32, 87, 211)
N-Methyldendrobinium	$(C_{17}H_{28}NO_2)^{+}$ Undetermined		Weak muscarinic and nicotinic					(140)
N-Methylveratrinium.........	$(C_{33}H_{52}NO_9)^+$ Undetermined	+			>100			(211)
N-Amylveratrinium.........	$(C_{37}H_{60}NO_9)^+$ Undetermined	⊕	Convulsant					(211)

animals. They reported that they were unable to make any correlation between chemical structure and paralyzing activity. Some of the most effective and least toxic of the ethers are listed in table 20. α-(*o*-Tolyl)glycerol ether, which has been given the name myanesin, is the most effective and has the greatest margin of safety.

TABLE 20

α-Glycerol ethers

$ROCH_2CH(OH)CH_2OH$		TOXIC DOSE MICE LD50 SC	PARALYZING DOSE MICE PD50 SC	THERAPEUTIC INDEX MICE LD50/PD50
Ether	R			
		mg./kg.	*mg./kg.*	
Butyl	C_4H_9—	2800 ± 150	1480 ± 54	1.89
Amyl	C_5H_{11}—	2000 ± 100	870 ± 49	2.30
Isoamyl	$(CH_3)_2CHCH_2CH_2$—	2100 ± 130	1240 ± 80	1.69
Hexyl	C_6H_{13}—	2230 ± 50	1060 ± 70	2.15
Phenyl	C_6H_5—	1680 ± 65	920 ± 98	1.82
p-Chlorophenyl		920 ± 86	420 ± 46	2.19
2,4-Dichlorophenyl		840 ± 44	540 ± 53	1.55
p-Bromophenyl		1160 ± 57	840 ± 44	1.38
o-Tolyl		1000 ± 56	325 ± 20	3.07
m-Tolyl		1470 ± 89	570 ± 51	2.58
p-Tolyl		1270 ± 61	530 ± 39	2.39
p-Ethylphenyl		1450 ± 67	820 ± 38	1.77
p-Methoxyphenyl		1610 ± 50	940 ± 74	1.72

The action of myanesin has been shown to be partially curare-like but mostly a depression of reflexes in the spinal cord (9, 10). That the action is somewhat curare-like is shown by the action of high concentrations on nerve-muscle preparations and the weak antagonism of physostigmine and prostigmine toward it. Large and nearly lethal doses are necessary to produce curare-like actions. Physostigmine and prostigmine accelerate the recovery of animals from myanesin paralysis, but do not abolish the effect of lethal doses of the drug. This suggests that the curare-like action accounts for only part of the effect produced.

The depressant action on the central nervous system is shown by the antagonism to convulsions produced by central nervous system stimulants. Myanesin does not appear to act on the brain, as it does not effect consciousness; hence it is not an anesthetic. In minimum paralyzing doses, myanesin appears not to affect blood pressure or respiration. With sufficiently large doses, death is due to respiratory failure.

Table 21 gives the periods of induction and the duration of paralysis for various doses of myanesin given intraperitoneally in mice. As shown in this table, the duration of paralysis is relatively short, but repeated doses show no cumulative effects, and tolerance is not built up.

TABLE 21

Duration of myanesin paralysis of mice

DOSE	PARALYZED	DIED	MEAN DURATION OF INDUCTION	MEAN DURATION OF PARALYSIS
mg./kg.	*per cent*	*per cent*		
150	0	0		
175	65	0	2 hr. ± 6 min.	12 hr. ± 1 hr. 42 min.
200	70	0	2 hr. ± 6 min.	13 hr. ± 4 hr. 18 min.
225	90	0	1 hr. 48 min. ± 12 min.	23 hr. ± 4 hr. 12 min.
300	100	0	1 hr. 36 min. ± 12 min.	25 hr. ± 2 hr. 48 min.
350	100	0	1 hr. 12 min. ± 6 min.	56 hr. ± 6 hr. 42 min.
500	100	5	48 min. ± 2 min.	61 hr. ± 12 hr. 42 min.
550	100	35		
600	100	45	48 min. ± 6 min.	120 hr. ± 4 hr. 18 min.
650	100	60		

Mallinson (145) investigated myanesin as a possible curare substitute in clinical use. He observed that the injection of 13 mg. per kilogram of body weight in a conscious patient caused no narcosis, although some is produced in animals. A dose of 27 mg./kg. in a patient produced some weakness of limbs and full abdominal relaxation without narcosis. The action of myanesin is enhanced by pentothal, so that full abdominal relaxation is easily obtained in man in doses of 10–15 mg./kg.

In therapeutically effective doses, there has been no evidence of toxic effects on any organ of the body. No effect has been noted on the tonus and contraction of intestinal muscle. Myanesin has well-marked advantages over curare in certain applications, having a much greater margin of safety and bringing about relaxation without distress. It is much more effective with barbiturate anesthesia than curare, apparently enhancing the action of the barbiturates.

V. SUMMARY

1. The peripheral curare paralysis is commonly associated with onium compounds, of which quaternary ammonium salts are the most effective.

2. A few nitrogen compounds which are not quaternary possess weak curare action. In general, the conversion of such a compound to a quaternary compound greatly increases the curare action.

3. The erythrina alkaloids, which contain a tertiary nitrogen common to two rings, possess a pronounced curare action. Conversion of this nitrogen to a quaternary nitrogen abolishes the curare activity. This is the only class of compounds which loses curare activity on conversion of a tertiary nitrogen to a quaternary nitrogen.

4. The length of the alkyl groups on the quaternary nitrogen has an effect on the intensity of curare action. Tetraethylammonium salts are less effective than tetramethyl, but the effectiveness is again increased with the tetrapropyl and tetrabutyl derivatives. In the series of alkyltrimethylammonium salts, the maximum effectiveness is reached with the butyl and amyl derivatives; in the quininium derivatives, the maximum is reached with the amyl derivative; and the curare action increases from the methyl to the butyl derivative of quinolinium salts.

5. The replacing of one alkyl group of tetraalkylammonium salts with a chain containing a phenyl group (benzyl or β-phenylethyl) reduces the muscarinic and nicotinic actions. Benzyltriethyl- and β-phenylethyltriethylammonium salts possess pure and pronounced curare activity.

6. The replacing of an alkyl group on a quaternary nitrogen with an aryl group reduces the curare activity.

7. The benzyl group is frequently associated with paralyzing action. In pyridinium, strychninium, coniinium, and brucinium salts, the *N*-benzyl derivatives have the most intense curare actions; further, 1-benzylisoquinolines have relaxing actions, whereas the same isoquinolines without the benzyl group may even cause contractions. The curare alkaloids, which possess a very pronounced peripheral paralyzing action, are of the bisbenzylisoquinoline type.

8. The degree of unsaturation of a ring containing the nitrogen, quaternary or otherwise, influences the intensity of the curare action. Piperidinium, tetrahydroquinolinium, and tetrahydroisoquinolinium salts have more intense curare-like actions than the corresponding pyridinium, quinolinium, or isoquinolinium salts. The canadinium salts, which have a quaternary nitrogen common to two saturated rings, possess pronounced curare activity. However, quaternary salts of palmatine, columbamine, and jatrorrhizine, which differ from canadine in that one of the rings which contains the quaternary nitrogen is unsaturated, exhibit a central paralysis rather than a peripheral one. In general, all of the really effective curare-like compounds have the nitrogen present in a saturated ring.

9. When a compound containing one nitrogen in an unsaturated ring and one in a saturated ring has both nitrogens quaternary, the compound is less effective than when only the nitrogen in the saturated ring is quaternary. This is shown in nicotinium and quininium derivatives.

10. The methoxyl group enhances curare action. Methylation of the two free hydroxyl groups in *d*-tubocurarine chloride greatly enhances its paralyzing action, whereas ethylation decreases and butylation abolishes the action. A methoxyl group in the 6-position enhances the curare action in quinolinium salts. The quininium salts are somewhat more effective than cinchoninium salts, the former containing a methoxyl group in the 6-position. β-Erythroidine and other erythrina alkaloids contain methoxyl groups.

11. When the conversion of a compound to a quaternary nitrogen compound produces two isomers, the higher-melting or β-isomer is invariably more effective than the lower-melting or α-isomer. This is true in numerous quaternary derivatives of coniine, conhydrine, and canadine, and in the tetrahydroerythroidine derivatives.

12. The sulfoacetic acid group enhances curare activity in some of the erythrina alkaloids.

13. The replacing of oxygen in choline with sulfur greatly enhances the curare action and abolishes the stimulating nicotinic action.

14. Certain α-glycerol ethers exhibit paralyzing actions. Of those tested, α-(*o*-tolyl)glycerol ether has the strongest action. These compounds do not possess a true curare-like action, but are the only compounds which do not contain nitrogen that have been reported to have possible therapeutic value as paralyzing agents.

15. The calabashcurarines, of unknown structure, are the most effective compounds reported. Nitration and bromination in some cases markedly increase their activity.

16. Curare alkaloids, erythrina alkaloids, quininium salts, and prostigmine have been used clinically for producing relaxation of muscles in various types of neuromuscular disorders involving spasm or contraction.

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RADIOACTIVE ISOTOPES AS INDICATORS IN BIOLOGY

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I. INTRODUCTION

Artificial radioactivity has come to be such a part of daily thought that it is difficult to introduce a review of the applications of radioactive isotopes as tracers in biology in terms which are adequate to the situation and not already common knowledge. It is necessary, however, to temper such general information with a critical analysis of the scope and limitations of the tracer technique.

The essential property which is the basis of all tracer applications of radioactive elements is that the tracer isotope possesses the same chemical properties as the naturally occurring stable isotopes of the particular element, while having a distinctive physical property, subject to measurement under properly selected conditions, which is independent of the chemical transformations it may undergo.

The radioactive isotopes are more generally useful as tracers than the separated heavy stable isotopes. The latter are available in only a few cases, and need to be converted to gases for determination of their relative abundance. There are available radioactive isotopes of practically all the elements of biological interest, and in most cases the measurement of very small amounts of such materials, preferably in the solid state, is relatively simple.

Although it is possible in some instances to obtain a practically pure radioactive isotope, the material used as a tracer in the usual case contains only a small amount of radioactive isotope in a large amount of ordinary stable isotope as carrier. The specific activity, the ratio of the number of radioactive atoms to the total number of atoms of that element present, is therefore rather low. For most purposes this is unimportant, since the comparison made is that of the relative specific activities of the substances isolated from the tissues with that of the material administered to the experimental animal. The relative specific activities are usually stated in arbitrary units, rather than in terms of the curie, the absolute unit of radioactivity. The curie is defined as the number of disintegrations per second from 1 g. of radium; the figure generally given for this is 3.7×10^{10}. The amounts used in tracer experiments are of the order of millicuries or, more commonly, microcuries. The smallest amount of radioactive material which can be measured with reasonable accuracy is of the order of 10^{-5} microcurie. This may represent as little as 10^{-8} microgram of the radioactive isotope.

The property by which radioactivity is detected and measured is that of producing ionization in gases. For a full discussion of the various types of measuring instruments and the properties of the different types of radiation, the review of artificial radioactivity by Seaborg (252) should be consulted. The principal types of measuring instrument are the electroscope, the integrating electrometer attached to an ionization chamber, and the Geiger–Müller counter. In the first two types named, the measurement is made in terms of the rate of movement of a quartz fiber across a scale. In the Geiger–Müller counter, which is the most sensitive type of instrument, each single disintegration is converted to an electrical discharge. This is amplified by a vacuum-tube circuit to actuate a mechanical recorder of some type. The counter tube consists essentially of a chamber containing a hollow metal cylinder cathode with a very thin wire anode coaxial with the cylinder. The chamber contains a gas or mixture of gases under somewhat reduced pressure. Those designed for counting beta particles usually have a thin window of glass, mica, or aluminum foil opposite the open end of the cylinder cathode. The samples to be measured are placed as close to this window as is feasible, and always in the same geometric relation to it.

Beta particles have a much greater tendency to produce ions and thereby lose energy than do the electrically neutral gamma rays. Their path is therefore much shorter, and the losses through scattering and absorption in the air space between the sample and the window, and absorption by the window itself, may become quite appreciable. This is particularly the case with the low-energy radiations which characterize radioactive isotopes of long half-life, such as C^{14} and S^{35}. In such cases there is also considerable self-absorption in the material containing the radioactive isotope, especially if this contains atoms of higher atomic number than those undergoing the disintegration. For the measurement of these isotopes of low energy of disintegration, special techniques are necessary. The principles involved in such measurements have been discussed by Libby (174).

Any measurements of radioactivity must be corrected for "background" ionization or counting rate arising from the effects of cosmic rays. This background ionization is a function of the volume of the ionization chamber of the electroscope or electrometer, and of the surface of the cylinder cathode of the Geiger–Müller tube. The ionization or counting rate from the sample being measured is a function of the solid angle from it subtended by the ionization chamber. On this account, the background correction may be quite high relative to the activity of weak samples. The accuracy of the measurement is proportional to the square root of the number of disintegrations recorded. The statistical error of the measurement is usually from 3 to 5 per cent, and higher with weak samples.

✓The radioautograph technique has certain applications in tracer studies. For this, the material is placed in contact with a photographic or x-ray film, and after a suitable exposure time, which may be several days, the film is developed. The silver deposits correspond to the location of the radioelement in the material. The method has been used rather extensively, especially in conjunction with histological studies, in determining the localization of radioiodine within the thyroid gland.

The possible duration of a tracer experiment, from the administration of the tracer substance to the completion of the measurements on material isolated from the experimental animal, is a function of the half-life of the radioelement. Experiments may extend over a period equal to four or five times the half-life without offering any great technical difficulties, but when the half-life is short, e.g., the 21-min. half-life of C^{11}, the scope and duration of tracer experiments are quite limited.

The total amount of radioactive material used in a biological experiment must not be so great that the general radiation effect is sufficient to produce alterations in functioning of the tissues of the experimental animal. The point was raised very early (20) that such tracer experiments would be invalid because of this general radiation effect and the consequent alterations in cellular function. It was soon shown (212) in experiments on *Nitella* that the permeability of the cell membrane to ions is not affected by concentrations of radioactivity below 1 millicurie per liter. This concentration is very much greater than that needed for most biological tracer experiments. However, it is well to bear in mind the general radiation effects, particularly in experiments of long duration.

One limitation on tracer experiments with organic compounds arises from the enormous energy release that accompanies the formation of a radioactive atom. This usually results in the rupture of the bonds that hold the atom in combination, especially if the linkages are non-ionic. It is therefore necessary to obtain the radioactive isotope by bombardment of an inorganic substance, and then use this material for the synthesis of the desired organic compound. With the increasing use of C^{14} in tracer experiments, the development of syntheses which permit the placing of this tracer in the desired position in the molecule will become a challenge to the ingenuity of the organic chemist.

There is still another method of making organic derivatives containing a traceable atom: the introduction of a radioactive halogen substitutent into an aromatic ring. In any such case, the question must be asked whether the presence of the substituent will alter the metabolic fate of the parent compound. More properly, the question becomes the point at which the halogen substituent may be removed from its position and thus cease to act as tracer for the original substance.

In cases where the nature of the compound is such that laboratory synthesis is impossible, for example, the plasma proteins, attempts have been made to obtain tracers by feeding compounds containing the desired radioelement. The enormous dilutions undergone in the metabolic processes that take place have been found to render the method unworkable in general.

An appreciable number of the early experiments with radioactive tracers were purely descriptive, and had little reference to whether the data obtained could contribute materially to knowledge of the dynamics of living matter. Still others were made without regard to whether the tracer approach was capable of yielding any information of critical value that was not as readily obtainable by ordinary experimental approaches. Such a situation arises whenever a new experimental tool is developed. It is only natural that the new technique be applied without taking cognizance of its inherent limitations. In fact, it sometimes happens that such experiments are the best means of calling attention effectively to the limitations to which the technique is subject.

The nature of many of the problems to which the radioactive isotope technique has been applied is such that the emphasis must fall on the biological aspects, rather than on the strictly chemical ones. The attempt has been made to select, from the large mass of literature available, those experiments which illustrate the particular field of usefulness of isotopic tracers in the study of dynamic processes within the living organism.

II. CARBON

The radiocarbon first discovered, C^{11}, has a half-life of only 21 min.; consequently a tracer experiment with it must be completed within 5 hr. after the cessation of bombardment of the target substance by the cyclotron. This includes the conversion of the carbon dioxide formed into an organic compound, administration of this to the experimental animal, isolation of the metabolic products formed, and determination of their radioactivity. In the counting, correction must be made not only for the self-absorption, but also for the falling off in the counting rate given by a sample during the few minutes necessary for making the measurements. In view of these limitations, the noteworthy results that have been obtained by the use of this isotope are all the more remarkable.

The other radiocarbon, C^{14}, represents the other extreme in half-life. The most probable value seems to be in the neighborhood of 5000 years. Thus, decay during the lifetime of an investigator is negligible, and material containing this isotope could conceivably be recovered and used again, subject to the limitation of dilution with ordinary carbon in the experimental procedures. The isotope is readily available from the operation of the uranium pile, both in the form of barium carbonate and as an increasing number of organic compounds. However, there are technical difficulties in its use which are by no means inconsiderable. Owing to the low energy of disintegration, there is a high self-absorption correction, and also a low efficiency of counting by the Geiger–Müller tube. This results from the scattering and absorption through even a few millimeters of air between the sample and the window, and great absorption by even the thinnest of windows (173).

Two methods have been proposed for overcoming this difficulty. Both depend on measuring the radiation from material in the form of $C^{14}O_2$. Henriques and Margnetti (125) introduce the gas into a quartz ionization chamber attached to a Lauritzen electroscope, and Miller (199) introduces it into the gas volume of a specially constructed Geiger–Müller tube. Carbon dioxide is notoriously unsuited for the gas in such counter tubes because of the lack of voltage plateau over which the counting rate is practically constant. Miller overcomes this by introducing a measured amount of carbon disulfide into the tube after the introduction of the carbon dioxide. It is stated that this gives a good plateau suitable for accurate counting, and that the counting rates obtained are perhaps one hundred times as much above background as would be the case when the same absolute amount of C^{14} as barium carbonate is measured by the ordinary Geiger–Müller counter technique. Both of these methods require extreme care in transferring the gas sample to the chamber and in removing it prior to the introduction of the next sample.

Despite these technical difficulties, C^{14} will probably prove to be one of the most useful tracer isotopes. The possibilities for its use in the study of intermediary metabolism are almost unlimited. Together with the separated stable heavy isotope, C^{13}, it can be used to establish the mechanism of many reactions where ordinary experimental approaches cannot do more than give indications of possibilities. The design of such experiments must be carefully thought out, and careful evaluation of both the experimental procedure and the data obtained will be necessary to establish whether the experiment is capable of demonstrating the point.

An example of the type of experiment in which C^{14} will probably be of greatest value is the recent demonstration by Gurin and Delluva (102) that phenylalanine is the precursor of epinephrine. They prepared the former compound with C^{14} in the carboxyl and alpha positions, injected this in rats, and after 3 days isolated the epinephrine from the adrenals. To obtain a crystalline product, it was necessary to add a relatively large amount of ordinary epinephrine in the isolation procedure, to act as carrier. The product isolated contained C^{14}, and it was shown by oxidation with periodic acid that this was all present in the terminal carbon of the aliphatic side chain of the epinephrine.

The major portion of the work that was done with C^{11} has been concerned with the reactions by which carbon dioxide is incorporated into organic compounds by living cells. The great accomplishment has been the demonstration that this type of reaction is by no means limited to the photosynthetic reaction in green plants, but also takes place in mammalian tissues.

The field of photosynthesis has been thoroughly explored in the book of Rabinowitch (226), and Wood (283) has reviewed non-photosynthetic carbon dioxide incorporation reactions. The use of isotopic carbon in the study of intermediary metabolism has also been reviewed fairly recently, by Buchanan and Hastings (31). Developments since these were published, and differences in interpretation of the data obtained, make it desirable to present certain aspects of the material in considerable detail.

The tracer experiments on photosynthesis were carried out with C^{11}, and the data obtained and conclusions drawn from them must be regarded as only preliminary. Experiments on barley seedlings (236) showed incorporation of carbon dioxide into the carbohydrates and to a very limited extent into the chlorophyll fractions, but no short-chain carbon compounds could be isolated which might serve as possible intermediates. Repetition of the experiments with the green alga *Chlorella*, which has a much higher rate of photosynthesis, led to indications that the initial stage, which is reversible and independent of light, is the incorporation of carbon dioxide into a compound of molecular weight between 1000 and 1500 which has the properties of a carboxylic acid. The reaction which is catalyzed by light appears to be the reduction of this acid to a primary alcohol (237, 238, 239). There were no indications obtained of any simple compounds which might be intermediates in the photosynthetic reaction.

There have been a considerable number of tracer experiments on bacterial metabolism, many of which deal with the carbon dioxide incorporation reaction first described by Wood and Werkman (285, 286). These investigators were able to demonstrate conclusively, and without the help of tracer isotopes, the incorporation of carbon dioxide into a three-carbon-atom compound, with the formation of a four-carbon-atom chain. In the anaerobic fermentation of glycerol to propionic acid by propionic acid bacteria, succinic acid is formed. By the use of $C^{13}O_2$ in the system, they were able to show that the carbon dioxide absorbed is present only in carboxyl groups of the succinic acid (287, 288). The mechanism postulated by Wood and Werkman for the reaction is the following:

$$CH_3COCOOH + C^*O_2 \rightleftarrows HOOC^*CH_2COCOOH \quad (1)$$

$$HOOC^*CH_2COCOOH + 2H \rightleftarrows HOOC^*CH_2CHOHCOOH \quad (2)$$

$$HOOC^*CH_2CHOHCOOH \rightleftarrows HOOC^*CH{=}CHCOOH + H_2O \quad (3)$$

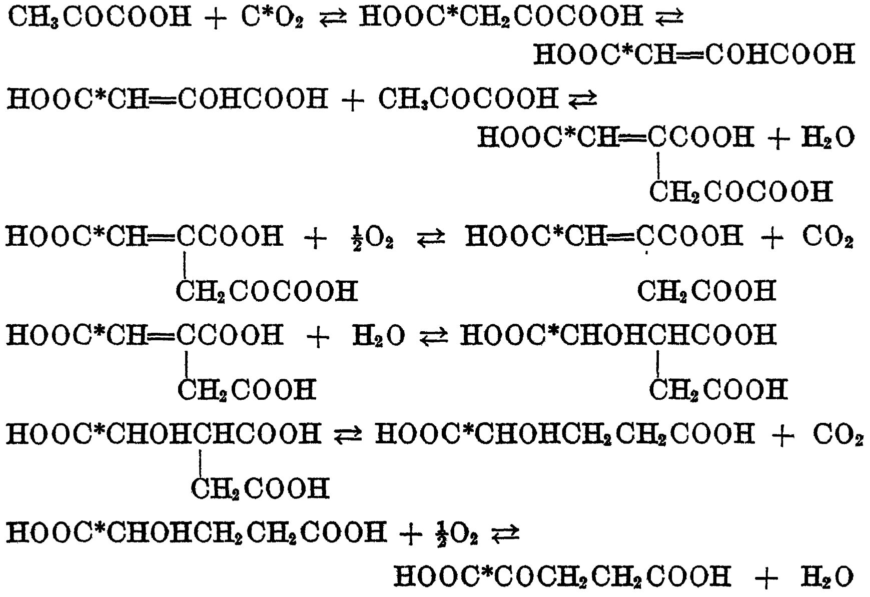
$$HOOC^*CH{=}CHCOOH + 2H \rightleftarrows HOOC^*CH_2CH_2COOH \quad (4)$$

By the use of C^{11} it has been shown (32) that the Wood and Werkman reaction is reversible. It has been demonstrated with C^{11} or C^{14} in three species of molds (80) and a protozoan organism (273). It has also been demonstrated in cell-free extracts of liver (67), and the data of Hastings and his collaborators (44, 260, 274) on the formation of liver glycogen in rats fed lactic acid are best interpreted on the basis that this reaction also takes place under these circumstances.

The mechanism of the Wood and Werkman reaction is apparently not as simple as that indicated in reaction 1, as Utter and Wood (271) found in extracts of liver tissue that the reaction takes place only in the presence of adenosine triphosphate (ATP). They suggest that this compound phosphorylates pyruvic acid, and that it is the phosphopyruvic acid which incorporates the carbon dioxide. Buchanan and Hastings, on the other hand, postulate direct incorporation into pyruvic acid, with phosphorylation taking place subsequently (31).

Other types of carbon dioxide incorporation reactions occurring in bacterial metabolism have been studied with radioactive carbon as tracer by Barker and his coworkers (14, 16, 17, 19) and by Foster *et al.* (80). In addition, Barker (18) showed by the use of butyric acid containing C^{14} in the carboxyl group that the conversion of this to caproic acid by *Cl. kluyveri* in the anaerobic fermentation of ethanol was brought about by condensation of the butyryl radical with the methyl carbon of acetic acid, rather than the reverse condensation. This was shown by the absence of C^{14} from the carboxyl group of the caproic acid formed, and by its presence elsewhere in the carbon chain.

Another type of carbon dioxide incorporation reaction in which the tracer technique was needed both for the demonstration of its occurrence and for the elucidation of the mechanism, is the formation of α-ketoglutaric acid from pyruvate by pigeon liver mince under aerobic conditions. On balance, carbon dioxide is evolved by this system. Evans and Slotin (67) used C^{11}, and Wood *et al.* (289) used the heavy stable isotope, C^{13}, to demonstrate that the carbon dioxide incorporated was present in the carboxyl group adjacent to the carbonyl. Wood *et al.* (288) have postulated the following modification of the Krebs tricarboxylic acid cycle to account for the experimental findings:



$$CH_3COCOOH + C^*O_2 \rightleftarrows HOOC^*CH_2COCOOH \rightleftarrows HOOC^*CH{=}COHCOOH \qquad (1)$$

$$HOOC^*CH{=}COHCOOH + CH_3COCOOH \rightleftarrows HOOC^*CH{=}\underset{\substack{|\\ CH_2COCOOH}}{C}COOH + H_2O \qquad (5)$$

$$HOOC^*CH{=}\underset{\substack{|\\ CH_2COCOOH}}{C}COOH + \tfrac{1}{2}O_2 \rightleftarrows HOOC^*CH{=}\underset{\substack{|\\ CH_2COOH}}{C}COOH + CO_2 \qquad (6)$$

$$HOOC^*CH{=}\underset{\substack{|\\ CH_2COOH}}{C}COOH + H_2O \rightleftarrows HOOC^*CHOH\underset{\substack{|\\ CH_2COOH}}{C}HCOOH \qquad (7)$$

$$HOOC^*CHOH\underset{\substack{|\\ CH_2COOH}}{C}HCOOH \rightleftarrows HOOC^*CHOHCH_2CH_2COOH + CO_2 \qquad (8)$$

$$HOOC^*CHOHCH_2CH_2COOH + \tfrac{1}{2}O_2 \rightleftarrows HOOC^*COCH_2CH_2COOH + H_2O \qquad (9)$$

Although none of these intermediates appears to be symmetrical, there are reasons why the scheme may not be an adequate explanation for the appearance of the labeled carbon in only one carboxyl group. On purely chemical grounds, the aconitic acid formed in reaction 6 might be expected to show a tautomeric shift of the double bond, and the orienting forces should produce hydration of this compound to give symmetrical citric acid rather than unsymmetrical isocitric. Since the tissues contain enzymes which maintain an equilibrium between citric, isocitric, and aconitic acids, it might be anticipated that the incorporation of the labeled carbon as carbon dioxide by this set of reactions would result in the labeling being present in both carboxyl groups of the α-ketoglutaric acid. Further study of this system seems to be indicated.

Evans and Slotin noted in their experiments that considerable C^{11} was present in a fraction which gave reactions characteristic of α-amino acids. They were unable to isolate any compounds from this fraction, on account of the short half-life of the isotope. Recently Anfinsen *et al.* (3a) have published a preliminary report on similar experiments on liver slices incubated with $C^{14}O_2$, in which they found that practically all of the C^{14} incorporated into the proteins was present in the dicarboxylic amino acids. It may be postulated that these were derived from secondary reactions of the α-ketoglutaric and oxaloacetic acids formed in the primary incorporation reactions, as liver is known to contain an active transaminase system for the interconversion of these compounds and the corresponding glutamic and aspartic acids (40).

One of the most interesting carbon dioxide incorporation reactions that has been studied by the isotope technique is that involved in the formation of liver glycogen when lactic acid is fed to the fasted rat. Hastings and his coworkers (44, 260, 274) have shown by the use of C^{11} that the glycogen deposited under these conditions contains small amounts of the tracer, whether this was present in the carboxyl or α,β-carbon of the lactic acid fed, or was administered as $NaHC^{11}O_3$ during the absorption of ordinary lactic acid. The glycogen formed in the liver was equivalent to about one-third the lactic acid fed, and the radioactivity present was from 0.6 to 3.2 per cent of that administered. The smallest amount was found in the $NaHC^{11}O_3$ experiments, and the highest when the tracer was present in the α,β-positions.

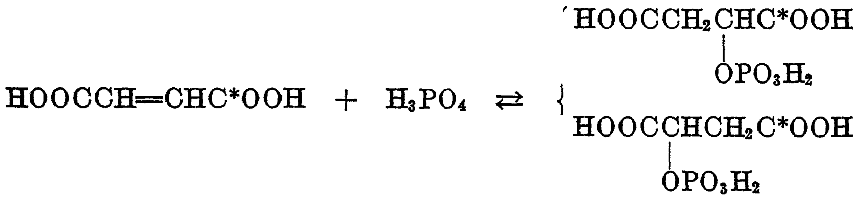
The experimental findings were accounted for on the basis of the occurrence of the Wood and Werkman reaction, reduction of the oxaloacetic acid formed to fumaric acid, phosphorylation of this, and decarboxylation to phosphopyruvic acid. This circuitous method of formation of phosphopyruvic acid was postulated by Kalckar (150) and Lipmann (177). The phosphopyruvic acid was considered by Hastings to undergo the reversal of the phosphorylating glycolysis, ultimately yielding glycogen. The series of reactions shown below is based on the postulates referred to, and is given first for lactic acid with the labeling in the carboxyl carbon, and then with α,β-labeled lactic acid. The phosphorylation of a dicarboxylic acid rather than that of pyruvic acid directly seemed called for by the finding of Meyerhof *et al.* (198) with P^{32} in muscle enzyme systems that the dephosphorylation of phosphopyruvic acid is irreversible. Lardy and Ziegler (161) have reported tracer experiments in a rather complicated system, in which they found some P^{32} uptake in the formation of phosphopyruvic acid. However, even if this indicated direct reversal of the reaction should be established, and the series of reactions given below should therefore require considerable modification, it would still be necessary to postulate the formation and decarboxylation of dicarboxylic acids in order to account for the experimental results obtained by Hastings and his coworkers.

$$\mathrm{CH_3CHOHC^*OOH} + \tfrac{1}{2}\mathrm{O_2} \rightleftarrows \mathrm{CH_3COC^*OOH} + \mathrm{H_2O} \tag{10}$$

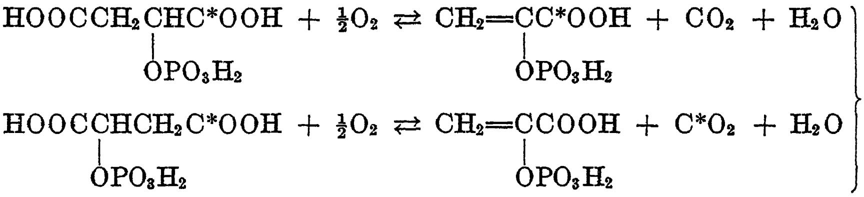
$$\mathrm{CH_3COC^*OOH} + \mathrm{CO_2} \rightleftarrows \mathrm{HOOCCH_2COC^*OOH} \tag{1a}$$

$$\mathrm{HOOCCH_2COC^*OOH} + 2\mathrm{H} \rightleftarrows \mathrm{HOOCCH_2CHOHC^*OOH} \tag{2a}$$

$$\mathrm{HOOCCH_2CHOHC^*OOH} \rightleftarrows \mathrm{HOOCCH{=}CHC^*OOH} + \mathrm{H_2O} \tag{3a}$$

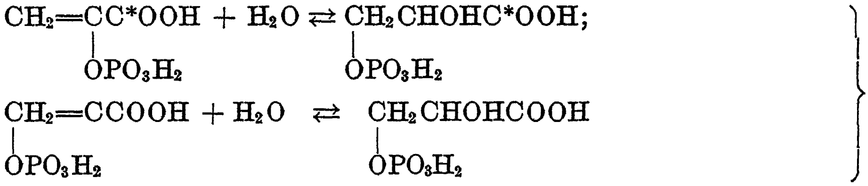


$$\mathrm{HOOCCH{=}CHC^*OOH} + \mathrm{H_3PO_4} \rightleftarrows \left\{\begin{array}{l} \mathrm{HOOCCH_2}\underset{\substack{|\\ \mathrm{OPO_3H_2}}}{\mathrm{C}}\mathrm{HC^*OOH} \\ \mathrm{HOOC}\underset{\substack{|\\ \mathrm{OPO_3H_2}}}{\mathrm{C}}\mathrm{HCH_2C^*OOH} \end{array}\right. \tag{11}$$

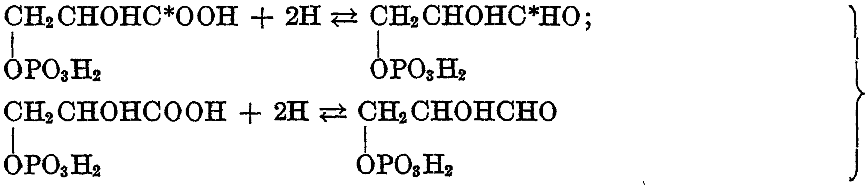


$$\left.\begin{array}{l} HOOCCH_2\underset{\substack{|\\ OPO_3H_2}}{C}HC^*OOH + \frac{1}{2}O_2 \rightleftarrows CH_2{=}\underset{\substack{|\\ OPO_3H_2}}{C}C^*OOH + CO_2 + H_2O \\ HOOC\underset{\substack{|\\ OPO_3H_2}}{C}HCH_2C^*OOH + \frac{1}{2}O_2 \rightleftarrows CH_2{=}\underset{\substack{|\\ OPO_3H_2}}{C}COOH + C^*O_2 + H_2O \end{array}\right\} \quad (12)$$

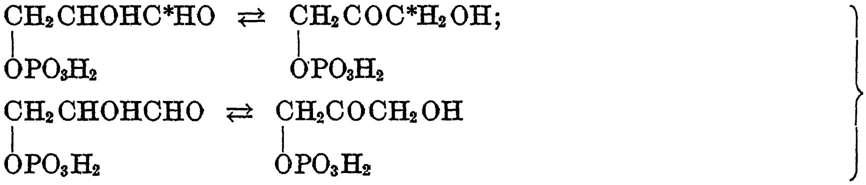
The use of ordinary lactic acid and labeled carbon dioxide would result in fumaric acid with the same labeling as shown above, and in the decarboxylation reaction half of the labeling would be lost, as is the case above, with the labeling originally present in the carboxyl group. In the condensation of the triosephosphate units resulting from the hydration and reduction of the phosphopyruvic acid, the statistical picture would be that half the triose molecules, and therefore each of the hexose units, would contain one C* atom. The reactions involved are shown below:



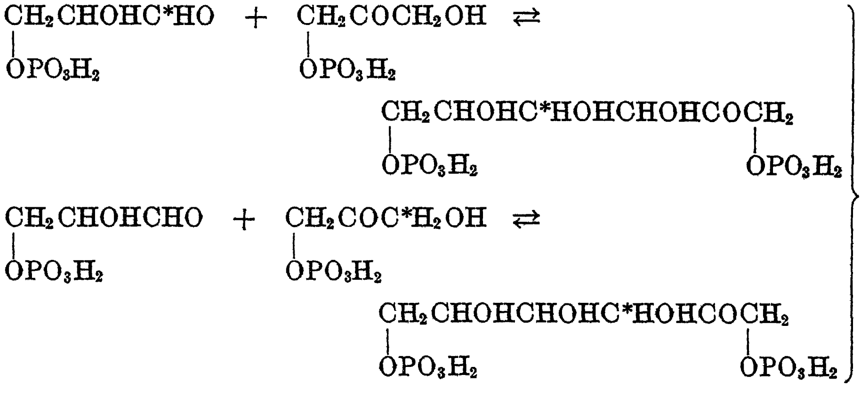
$$\left.\begin{array}{l} CH_2{=}\underset{\substack{|\\ OPO_3H_2}}{C}C^*OOH + H_2O \rightleftarrows \underset{\substack{|\\ OPO_3H_2}}{CH_2}CHOHC^*OOH; \\ \underset{\substack{|\\ OPO_3H_2}}{CH_2}{=}CCOOH + H_2O \rightleftarrows \underset{\substack{|\\ OPO_3H_2}}{CH_2}CHOHCOOH \end{array}\right\} \quad (13)$$



$$\left.\begin{array}{l} \underset{\substack{|\\ OPO_3H_2}}{CH_2}CHOHC^*OOH + 2H \rightleftarrows \underset{\substack{|\\ OPO_3H_2}}{CH_2}CHOHC^*HO; \\ \underset{\substack{|\\ OPO_3H_2}}{CH_2}CHOHCOOH + 2H \rightleftarrows \underset{\substack{|\\ OPO_3H_2}}{CH_2}CHOHCHO \end{array}\right\} \quad (14)$$



$$\left.\begin{array}{l} \underset{\substack{|\\ OPO_3H_2}}{CH_2}CHOHC^*HO \rightleftarrows \underset{\substack{|\\ OPO_3H_2}}{CH_2}COC^*H_2OH; \\ \underset{\substack{|\\ OPO_3H_2}}{CH_2}CHOHCHO \rightleftarrows \underset{\substack{|\\ OPO_3H_2}}{CH_2}COCH_2OH \end{array}\right\} \quad (15)$$



$$\left.\begin{array}{l} \underset{\substack{|\\ OPO_3H_2}}{CH_2}CHOHC^*HO + \underset{\substack{|\\ OPO_3H_2}}{CH_2}COCH_2OH \rightleftarrows \\ \qquad \underset{\substack{|\\ OPO_3H_2}}{CH_2}CHOHC^*HOHCHOHCO\underset{\substack{|\\ OPO_3H_2}}{CH_2} \\ \underset{\substack{|\\ OPO_3H_2}}{CH_2}CHOHCHO + \underset{\substack{|\\ OPO_3H_2}}{CH_2}COC^*H_2OH \rightleftarrows \\ \qquad \underset{\substack{|\\ OPO_3H_2}}{CH_2}CHOHCHOHC^*HOHCO\underset{\substack{|\\ OPO_3H_2}}{CH_2} \end{array}\right\} \quad (16)$$

The fructosediphosphate will thus contain equal amounts of C* in positions 3 and 4, and the statistical average content will be equivalent to one labeled carbon per hexose unit. The postulate that phosphopyruvic acid is formed directly, instead of by the Wood and Werkman reaction, would require that the glyceric aldehyde phosphate and dihydroxyacetone phosphate be labeled to the same extent as the lactic acid administered, and the fructosediphosphate thus would contain a statistical average of two labeled carbon atoms per hexose unit.

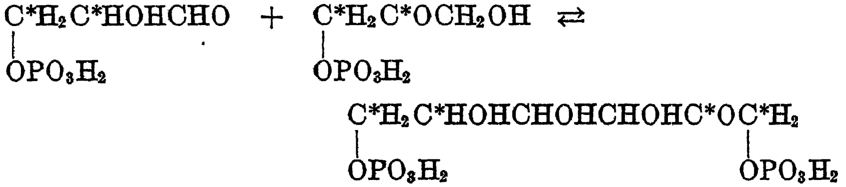
When the labeling agent is present in the α,β-positions instead of the carboxylic acid group, the degree of labeling of the hexose unit is independent of the occurrence of the carbon dioxide incorporation reaction. This can be seen from the following set of reactions:

$$C^*H_3C^*OCOOH + CO_2 \rightleftarrows HOOCC^*H_2C^*OCOOH \qquad (1b)$$

$$HOOCC^*H_2C^*OCOOH + 2H \rightleftarrows HOOCC^*H_2C^*HOHCOOH \qquad (2b)$$

$$HOOCC^*H_2C^*HOHCOOH \rightleftarrows HOOCC^*H{=}C^*HCOOH + H_2O \qquad (3b)$$

In the subsequent decarboxylation of this symmetrically labeled fumaric acid, no labeled carbon is lost, and the final condensation of the two triosephosphates becomes:



$$\underset{\overset{|}{OPO_3H_2}}{C^*H_2}C^*HOHCHO + \underset{\overset{|}{OPO_3H_2}}{C^*H_2}C^*OCH_2OH \rightleftarrows \underset{\overset{|}{OPO_3H_2}}{C^*H_2}C^*HOHCHOHCHOHC^*O\underset{\overset{|}{OPO_3H_2}}{C^*H_2} \qquad (16a)$$

The fructosediphosphate has four C* atoms, in positions 1, 2, 5, and 6. Vennesland *et al.* (274) performed the experiment with lactic acid prepared by the method of Cramer and Kistiakowsky (54). This involves reduction of $BaC^{11}O_3$ to BaC_2^{11}, conversion to acetylene, acetaldehyde, its cyanohydrin, and finally lactic acid. The C^{11} must be regarded as being equally distributed between the two carbons of the acetylene, and therefore equally between the α- *and* β-carbons of the lactic acid, rather than being present in the α- *or* β-position, as was assumed by Vennesland *et al.*

Since the experimental conditions were the same whether carboxyl-labeled or α,β-labeled lactic acid was fed, it is reasonable to assume that the lactic acid fed constituted the same fraction of the metabolic pool which gave rise to the liver glycogen. The data obtained with α,β-labeled lactic acid are independent of the occurrence of a carbon dioxide incorporation reaction, and can thus be used for the calculation of the contribution of the fed lactic acid to this metabolic pool. This is done by comparing the relative specific activities of the labeled carbon fed and found. The data of Vennesland *et al.* have been recalculated on the basis indicated above, and the average contribution of the lactic acid fed to the metabolic pool is found to be 14.3 per cent.

Similar calculations from the data on carboxyl-labeled lactic acid (44) indicate an average contribution of 11.6 per cent by the fed lactic acid to the metabolic pool on the basis of the Wood and Werkman reaction, and only 5.8 per cent if no such incorporation reaction is postulated. These calculations show that a carbon dioxide incorporation reaction is involved in the formation of liver glycogen from fed lactic acid in the fasted rat. They do not, of course, indicate whether the phosphorylation involved is that of some dicarboxylic acid intermediate, as assumed by Hastings and his coworkers, or of pyruvic acid directly, as postulated by Lardy and Ziegler (161).

The calculations just given present a suggestion of the possible quantitative significance of the carbon dioxide incorporation reaction in mammalian metabolism. It is obvious that a vast amount of work must be done before an assessment of the significance of such reactions under a wide range of conditions can be had. Such experiments can be carried out only with the use of tracer isotopes.

There is evidence from some recent experiments by Hastings *et al.* (120) that indicates direct combination of three-carbon-atom fragments as an alternative mechanism for the formation of the units which form liver glycogen. When rabbit liver slices were incubated with pyruvate and $C^{14}O_2$, the tracer content of the glycogen formed indicated that 10 per cent of its carbon was derived from carbon dioxide. These data can be taken as indicating that 60 per cent of the glycogen formation proceeded through the incorporation reactions, and 40 per cent by direct combination of three-carbon-atom units.

With glucose as substrate, 2 per cent of the glycogen carbon was found to originate in carbon dioxide, corresponding to 12 per cent of the glycogen arising through incorporation reactions under these conditions. These probably took place with pyruvate arising during the course of oxidation of carbohydrate. In the same way, the finding of Vennesland *et al.* (275) that some C^{11} was present in the liver glycogen deposited when fasted rats were fed glucose and injected with $NaHC^{11}O_3$ can be explained on the basis that the incorporation took place with pyruvate arising from lactic acid reaching the liver from the breakdown of muscle glycogen. The assumption of Buchanan and Hastings (31) that the data of Vennesland *et al.* indicate an obligate conversion of glucose to three-carbon-atom fragments which then undergo the Wood and Werkman reaction scarcely seems necessary.

The method indicated above for calculating the contribution of the metabolite fed to the metabolic pool which forms liver glycogen is not applicable to the experiments of Solomon *et al.* (260) in which ordinary lactic acid was fed to fasted rats and $NaHC^{11}O_3$ injected at intervals during the absorption period, nor to the similar experiments of Vennesland *et al.* (275) with glucose and $NaHC^{11}O_3$.

There still remains to be determined the total composition of the metabolic pool which goes to form liver glycogen when glucose or lactate is administered to the fasted rat. The major possibility is, of course, the fatty acids and their derivative ketone bodies. Buchanan *et al.* (30) have attempted to evaluate the contribution of the lower fatty acids to this metabolic pool, by administering acetic, propionic, and butyric acids containing C^{11} in the carboxyl group, together with glucose, to the fasted rat. The experimental procedure reduced the possible contribution of the fatty acids to a small fraction of the metabolic pool, as they were fed with more than their own weight of glucose, and the glycogen formed was equivalent to less than 20 per cent of the glucose fed. The method of calculation used did indicate to them that propionic acid did contribute directly, and acetic and butyric acids probably did contribute, to the metabolic pool, beyond the amount that could be expected on the basis of carbon dioxide from the oxidation of these acids during the absorption period. A recalculation of their data on the basis of relative specific activities of carbon fed and found fails to show definitely that these fatty acids were direct precursors of liver glycogen.

Wood and his collaborators have carried out experiments with fatty acids labeled with heavy carbon, C^{13}, which demonstrate that these do contribute to the formation of liver glycogen, and have also clarified the mechanism of the process to a very considerable extent. Their experimental conditions were such that the quantitative significance of this process under steady-state conditions cannot be evaluated. The first experiment consisted of feeding ordinary glucose to fasted rats and injecting $NaHC^{13}O_3$ (284). The glycogen isolated from the liver was subjected to hydrolysis, and part of the glucose was converted to methyl glucoside. By bacterial degradation of the glucose, and stepwise oxidation of the methyl glucoside with periodic acid, they were able to show that all the C^{13} excess was present in positions 3 and 4 of the glucose. Reference to reactions 1–3 and 13–16 will show that this is exactly the result to be anticipated on the basis of the Wood and Werkman reaction followed by a reversal of the pathway of the phosphorylating glycolysis.

The next step was the feeding of $C^{13}H_3C^{13}OOH$ (179). The liver glycogen isolated in this case had C^{13} excess present in all six positions. Since that in positions 3 and 4 came from the Wood and Werkman reaction, that in the remaining four positions could have come either from the acetic acid directly or from the methyl group alone. Positions 1, 2, 5, and 6 would be labeled if the triosephosphate molecules which condense to form the fructosediphosphate contain the labeling in the 2,3-positions, as shown in reaction 16a.

More recently (175) experiments with C^{13} present in the α,β- or carboxyl position of butyric acid have been reported. The glycogen obtained from either carboxyl- or β-labeled butyric acid contained C^{13} excess in only the 3,4-positions, while that from the feeding of the α-labeled acid contained C^{13} excess only in positions 1, 2, 5, and 6.

These experimental findings are all consistent with the hypothesis of Wood *et al.* (289) that the pathway for the conversion of the ketone bodies, and thus also the fatty acids, to glycogen is through a modification of the tricarboxylic acid cycle. The initial step is the condensation of acetate (or possibly acetyl phosphate) with oxaloacetic acid, yielding aconitic acid. The further series of reactions (6–9) would yield α-ketoglutaric acid, from which fumaric acid would be formed by oxidative decarboxylation and dehydrogenation. Since this is a symmetrical compound, the labeling agent originally present in the α-carbon of the acetic and butyric acids would be equally distributed between the two central carbons of the fumaric acid, and hence in the α,β-positions of the decarboxylation product. In the final condensation of the two triosephosphates, the labeling agent would be equally distributed between carbons 1, 2, 5, and 6.

These experiments indicate that when lactate is fed to the fasted rat, the principal source of the metabolic pool which goes to form liver glycogen is furnished by the ketone bodies which are being produced by the liver under these conditions. In this sense, and under these conditions, the conversion of fat to carbohydrate in the animal body has been demonstrated. It still remains to be ascertained whether ketone bodies are such quantitatively important precursors of liver glycogen in other species, and in the postabsorptive state. Properly designed experiments with either heavy carbon or radiocarbon are the only means which offer definite prospect for establishing the facts.

III. SODIUM, POTASSIUM, AND CHLORINE

The radioactive isotopes of these elements have given information concerning the passage of ions across capillary walls and cell membranes which could not be obtained without the use of such tracers. The experimental data show that such movements of ions are best explained in terms of active transfer rather than as simple physical diffusion processes, in the case of cell membranes and some capillaries.

The rate at which isotope equilibrium is established between plasma and the extracellular phase of the tissues is greatest in small animals. Such equilibrium is reached within 5 min. after the intravenous injection of $Na^{24}Cl$ in the rat (197), but requires about an hour in the dog (152). In the normal human subject the equilibration time is about 3 hr. (152). The capillaries of the choroid plexus have been found to be as freely permeable to cations as are those of the tissues generally. This has been shown in an extensive series of experiments by Greenberg *et al.* (98), in which the time course of the isotope concentration in freshly secreted cerebrospinal fluid was compared with that of plasma. The cations studied were sodium, potassium, strontium, and rubidium. The situation with respect to anions is much more complex. Bromide ion behaved like sodium ion, but iodide and phosphate ions were present in much lower concentration in the CSF than in plasma, at apparent equilibrium.

The capillaries within the brain substance show a very limited permeability to ions. This had been demonstrated by a variety of other techniques, with respect to cations. These are summarized in the review by Friedemann (85). It remained for the radioactive isotope technique to demonstrate that the anion-transfer rates are very low.

Determinations of the total extracellular phase of the body by the isotope dilution method with $Na^{24}Cl$ have generally given results in the human and in the laboratory animal which are comparable to those obtained by the thiocyanate method (99, 104, 152, 184, 204). The results of such determinations with $LiCl^{38}$ (185) and $NaBr^{80}$ (104) on laboratory animals have given comparable results also, but Moore (204) has reported that in the same human subject Cl^{38} was distributed through only about 70 per cent as much volume as Na^{24}.

There has been considerable discussion in the literature on the question of whether sodium ion is present within the cells of certain tissues. Experiments with $Na^{24}Cl$ have thrown some light on the matter. In the case of the testis, for instance, it has been found (184) that the time course of the uptake of sodium ion shows a rapid phase which corresponds to the equilibration between plasma and extracellular fluid, followed by a slow phase which indicates transfer across the cell membrane by osmotic work. A similar phenomenon has been shown in the muscles of rats which had been maintained on a diet low in either sodium (99) or potassium (126).

Studies with radioactive tracers on the passage of ions across the cell membrane of the erythrocyte have shown that chloride ion passes across this membrane quite rapidly (258), but the rates of transfer of sodium ion and potassium ion are quite low (41, 61, 103, 211). The experiments with K^{42} illustrate one pitfall encountered in the use of radioactive isotopes. Hahn, Hevesy, and Rebbe (103) first reported the extremely low exchange rate of 3 per cent in 24 hr. in the rabbit. Fenn and his coworkers (57, 214) found about 50 per cent exchange in 24 hr. in this species, and also reported that there were marked species differences in the transfer rate. Fenn has pointed out that the discrepancy could be accounted for by the presence of as little as 0.02 per cent sodium chloride in the potassium chloride subjected to bombardment by Hahn *et al.*, because the yield of Na^{24} per microampere hour of bombardment by deuterons is about 200 times that of K^{42}. Fenn and his coworkers freed their $K^{42}Cl$ from contaminating sodium by precipitation as perchlorate and ignition of this to the chloride.

These observations and a number of others with Na^{24} and Cl^{38} indicate that osmotic work is necessary for the transfer of ions across membranes, and that simple physical diffusion is inadequate to explain the observed rates of movement. For example, Visscher *et al.* (278) found transfer rates between the lumen of the ileum and the plasma to be far higher than those expected from simple diffusion, and not necessarily dependent on concentration gradients. Cope *et al.* (47) found that $Na^{24}Cl$ was absorbed at different rates from pouches of the body and the pyloric antrum of the stomach: per unit area of mucosa the pyloric region absorbed about one hundred times as much as did the body, and this high absorption rate continued during the active secretion of hydrochloric acid.

Other studies which indicate that the passage of ions across cell membranes involves osmotic work are those of Kinsey *et al.* (158) on the aqueous humor, and of Wills (282) on saliva. In these experiments Na^{24}, K^{42}, F^{19}, Cl^{38}, and P^{32} as phosphate were used. The data of Ussing (270) with Na^{24} on axolotls show that the rate of transport of this ion into the tissues can be increased by much as 200 per cent by the injection of the antidiuretic hormone of the posterior pituitary.

Flexner and his collaborators (76) have made an extensive study of the rate of transfer of $Na^{24}Cl$ across the placenta in a number of species. The transfer was found to be relatively slow in comparison with the rate of passage across the capillary wall. For example, only 4 min. are required to reach 90 per cent equilibrium between plasma and extracellular phase in the cat, but a similar degree of equilibrium between maternal and fetal plasma is reached only in 12–18 hr. The absolute transfer rate was found to be related to the number of cell layers in the placenta, and in most species the total sodium ion transfer during pregnancy was computed to be about twenty-five times the sodium content of the fetus at term. In contrast, the total transfer of phosphate across the placenta was found (281) to be only slightly in excess of that retained by the fetus.

Studies with $K^{42}Cl$ (70, 149, 215) have shown that potassium exchange between tissues and extracellular phase takes place at fairly rapid rates despite high concentration gradients. This applies to the heart, liver, and kidney. In striated muscle the exchange rate is slower, possibly because of the relatively low blood flow.

When $K^{42}Cl$ is administered by mouth or intraperitoneally, there is a brief period during which the specific activity of the potassium ion of liver exceeds that of plasma (70), after which the specific activity falls rapidly to that of the plasma potassium. The initial accumulation of potassium in the liver that these findings indicate had been shown earlier by Fenn (68) without benefit of radioactive tracers, but the time course of the relative specific activities of liver and plasma potassium can only signify that this accumulation takes place on the cell membrane, rather than within the cells. Teleologically, such a storage may be postulated to have the function of protecting the heart against the depressant action of a sudden influx of potassium ions into the plasma.

Another illustration of the value of the tracer technique in demonstrating ion-transfer effects that could not otherwise be shown is in connection with the finding by Fenn and Cobb (69), by ordinary experimental procedures, that prolonged stimulation of muscles of rats *in situ* results in net loss of potassium to the plasma. Repetition of the experiments with $K^{42}Cl$ by L. Hahn and Hevesy (105) and by Noonan *et al.* (216) showed that this loss of potassium took place in spite of a markedly accelerated rate of entry of this ion into the muscle cells. Noonan *et al.* ascribe this accelerated exchange to increase in blood flow rather than to change in permeability of the muscle cell membrane, as it was not seen in isolated frog muscle stimulated in Ringer solution containing $K^{42}Cl$. On the other hand, both these workers and Lyman (183) found an accelerated rate of exchange of potassium ion between plasma and denervated muscle which can best be explained on the basis of altered permeability.

Another example of a problem in this field which can be handled adequately only by the isotopic tracer technique is that of the state of sodium in bone. Kaltreider *et al.* (152) showed by the use of $Na^{24}Cl$ *in vivo* that bone contains a reservoir of sodium that exchanges only slowly with plasma sodium. This finding, and the additional observation that the sodium content of bone is rather high, are adequately accounted for by the showing by Hodge *et al.* (141) that ground bone *in vitro* adsorbs considerable sodium. The adsorption follows the Freundlich isotherm, and at body temperature and the concentration of sodium present in plasma, it is of sufficient magnitude to explain the sodium content of bone.

In plant materials it has been shown by the use of Na^{24}, K^{42}, and $Rb^{86,88}$ that both simple cation exchange and metabolic uptake of these ions takes place

(27, 28). The exchange is independent of temperature and oxygen tension, but the metabolic uptake takes place only in the presence of oxygen, is increased by exposure to light, and has a high temperature coefficient. There is also a related observation by Hevesy and Nielsen (138) that yeast cells show a more rapid exchange of K^{42} with the suspending medium during active fermentation than during the resting state.

IV. PHOSPHORUS

Compounds of phosphorus are of such great biological importance that it is fortunate that P^{32} combines the desirable features of relatively long half-life and high energy of disintegration. Almost half of the total number of papers on biological applications of radioelements as tracers describe experiments with P^{32}. The very first such paper, that of Chievitz and Hevesy (39) in 1935, was concerned with the distribution of labeled phosphate among the tissues of the rat.

The problems that have been studied with this tracer range from the demonstration of the mechanism of an enzyme reaction to the study of the effects of x-ray radiation on the rate of formation of nucleoproteins in the nuclei of tumor cells. The wealth of material available makes it necessary to limit the discussion to those matters in which the tracer technique has given definitive information not attainable by other experimental methods.

One limitation on the value of P^{32} as a tracer is that organic phosphate compounds injected into the animal undergo hydrolysis to inorganic phosphate in the process of absorption, so that their fate and distribution are not directly ascertainable (2, 37, 132, 235).

A. Enzyme reactions

The simplest system in which P^{32} has given definitive results not otherwise demonstrable is in the conversion of α-glycerophosphoric acid to the β-derivative. Chargaff (36) incubated the α-compound with alkaline phosphatase in the presence of P^{32} as inorganic phosphate. The β-compound formed contained no P^{32}; the reaction must therefore have been an intramolecular one. Meyerhof *et al.* (198) used a similar technique to show that the conversion of 3-phosphoglyceric acid to the 2-derivative also takes place intramolecularly. They also obtained evidence by this means that the enzymatic dephosphorylation of phosphopyruvic acid is irreversible. However, Lardy and Ziegler (161) have demonstrated with P^{32} that some of the tracer was taken up by the phosphopyruvic acid formed in muscle extract under certain conditions. While the conclusion they drew, that this reaction is reversible, may be correct, the enzyme system used was so complex and the P^{32} uptake by the phosphopyruvate was so low, that the point cannot be considered to be established.

B. Bone and teeth

There have been several investigations of the metabolism of phosphate in these structures by the tracer technique. One quite thorough study of the time course of the relative P^{32} contents of these in comparison with plasma inorganic phosphate was made by Manly *et al.* (186, 187). The conclusion drawn was that bone and teeth consist of a stable portion in which phosphate once deposited tends to remain indefinitely, and a labile portion which is in dynamic equilibrium with plasma inorganic phosphate. The subject has recently been reinvestigated by Neuman and Riley (214a) in the same laboratory. They find that exchange adsorption takes place on the surface of bone salt with great rapidity. Most of this process is complete within 2 hr. after the intravenous injection of tracer, and it involves about 20 per cent of bone. On this account, it is concluded that P^{32} is not particularly useful in studies on the deposition of bone in growth.

Hodge and his coworkers have made extensive studies of the adsorption of various ions on bone and teeth *in vitro* with radioelements as the adsorbed ion. Studies on phosphate (142, 145, 188), sodium (141), strontium (140), and fluoride (279) have shown that the process follows the Freundlich isotherm. In the cases of sodium and strontium, it is possible to account for the amounts normally present in bone on the basis of such adsorption.

There have been a number of studies on rickets in which P^{32} has been used, but in general the information obtained could have been inferred, if not necessarily clearly demonstrated, by ordinary experimental methods. As examples of this, the following may be cited: Cohn and Greenberg (42) found that the administration of vitamin D to rachitic rats resulted in a shift in distribution of the phosphate absorbed from the intestine, so that less exchanged with soft tissue phosphate and more was deposited in bone, and also there resulted decreased reëxcretion of phosphate into the intestine. Morgareidge and Le Fevre (202) found that the maximum increase in the P^{32} content of the metaphysis of the bones in rachitic rats which followed the administration of a single dose of vitamin D took place in from 54 to 72 hr. Histological examinations of tissues taken at this time showed healing of the lesions. Manly and Levy (189) gave a single dose of P^{32} phosphate to pregnant rats shortly before term, and found that the relative specific activity of the phosphate of the young at birth was comparable to that of the maternal soft tissues, rather than to that of the bones. This held whether the rats were on a normal or rachitogenic diet.

C. Mechanism of entry of phosphate into tissue cells

The entrance of phosphate into the cell interior from the extracellular phase is a considerably more complicated matter than the entry of cations. Most tissues contain higher concentrations of inorganic phosphate than is present in plasma, and still larger amounts are present in organic combination. When a dose of tracer phosphate is injected into an experimental animal, the distribution of the P^{32} found in the tissues is the resultant of the transfer across the cell membrane and the metabolic interchanges within the cell. On this account it is necessary to use caution in the interpretation of such experiments. Critical analysis of the data obtained on various tissues by this means indicates that simple diffusion processes are less adequate to account for the phosphate exchange between the cell and its environment than is the case with cations. It is necessary to postulate some enzymatic mechanism for bringing about the entry of phosphate. In the erythrocyte, for example, Eisenman *et al.* (61) found that the amount of phosphate transferred to the cell interior was entirely too great at 37°C. to be explained on the basis of diffusion, and also that the process had the high temperature coefficient characteristic of chemical reactions. In yeast cells, both Hevesy *et al.* (137) and Mullins (213) report that phosphate enters the cell only during active metabolism of carbohydrate, and that the rate of entry shows a high temperature coefficient.

The rate of exchange of phosphate between the brain and blood plasma is extremely slow in comparison with that of other tissues (10, 21, 184), and the uptake of P^{32} by the phospholipids of brain is very slow in the adult animal (34). In the new-born rat, however, the uptake by both total brain phosphate (88) and phospholipids (89) is many times the rate found in the adult animal. Slices of brain incubated with P^{32} phosphate show a fairly rapid incorporation of the tracer into the phospholipids (90), and the rate is increased considerably in the presence of glucose or other readily oxidizable sugar (249).

These results show that it is necessary to separate the metabolic interchanges between the various phosphorus compounds present within the cell, from the transfer of phosphate across the membrane. In brain, the metabolic interchanges apparently have a high rate, whereas the rate of transfer across the cell membrane is limited by the very low permeability of the brain capillaries.

The necessity for making this distinction is emphasized by the conflicting interpretations of data on these processes in heart and striated muscle. The experiments in point are those of Furchgott and Shorr (91) on slices of dog heart incubated with tracer phosphate, of Kalckar *et al.* (151) on intravenous injection of the tracer in rabbits, of Sacks and Altshuler (246) on the time course of the relative specific activities of the acid-soluble phosphorus compounds of heart and striated muscle in cats, and of Bollman and Flock (23) on the effect of prolonged circulatory occlusion on the subsequent uptake of P^{32} by muscles.

Furchgott and Shorr found that in incubation of heart slices at 37.5°C. the specific activities of the phosphocreatine (PC) and terminal phosphate group of the adenosine triphosphate (ATP) at equilibrium were about one-fifth that of the inorganic phosphate of the medium. They interpreted the data in terms of diffusion of inorganic phosphate into the cell interior, followed by rapid conversion to the organic compounds by the reactions of the phosphorylation cycle. It should be pointed out that this interpretation carries with it the implicit corollary that only one-fifth of the intracellular inorganic phosphate is available for such free diffusion across the cell membrane, while the entire amount is available for the interchange reactions with PC and ATP.

Kalckar *et al.* injected the tracer phosphate, after a short time chilled the hind legs of the animal, and then perfused one leg with ice-cold phosphate-free Ringer solution, in an attempt to wash all the P^{32} out of the extracellular phase, so that comparison could be made of the relative specific activities of intracellular inorganic phosphate and ATP. Most of the PC in the muscles underwent hydrolysis during the perfusion period. The experiments are subject to the criticisms that the anoxia and low temperature during the perfusion can hardly be expected to leave the permeability of the cell membrane unimpaired, that the hydrolysis of PC added to the inorganic phosphate a relatively large amount of material of low specific activity, and that the data show that the washing out of the extracellular inorganic phosphate was by no means complete. The experiments are therefore of no critical value for the determination of how phosphate enters the muscle cell.

The data of Sacks and Altshuler show that the highest specific activity found in the PC and ATP of the heart was less than one-fourth that of the plasma inorganic phosphate sampled at the same time, and that the specific activities of these compounds in muscle were only about one-tenth as high as those of heart. At no time was there any evidence that isotope equilibrium had been established between plasma phosphate and PC or ATP in either muscle or heart; 24 hr. after the injection of the tracer, the relative specific activities of PC and ATP in the heart were significantly higher than that of plasma phosphate. Such a situation could not obtain if phosphate entered the cell by simple diffusion; once isotope equilibrium had been established, there could not subsequently be any change of specific activities of plasma and intracellular phosphates with respect to each other. The conclusion drawn from these experiments was that phosphate entered the cell by formation on the membrane of organic phosphate compounds, so oriented spatially that the compound could enter the cell interior and then take part in metabolic interchanges with other phosphate compounds.

On this hypothesis, the equilibrium ratios of relative specific activities of plasma and intracellular phosphates, under conditions of constant P^{32} content of the plasma, would give a measure of the relative frequency of intracellular metabolic interchanges and those across the cell membrane. The slice experiments of Furchgott and Shorr approximate this condition and indicate for heart muscle a ratio of five intracellular exchanges to one across the membrane. The data of Sacks and Altshuler indicate a similar ratio in the intact heart, and by extension to the muscle, a ratio of some 50 to 100 intracellular exchanges for each one across the membrane. The situation is analogous to that found in brain by Fries and Chaikoff (88, 90): a high rate of metabolic interchange within the cell coupled with a low rate of transfer across the membrane. In the case of brain it is the capillary wall rather than the cell membrane which is the barrier to free exchange with plasma phosphate.

To explain the data on intact muscle by the hypothesis of free diffusion of phosphate ion across the cell membrane would require the postulate that only 1 or 2 per cent of the entire intracellular inorganic phosphate is available for the metabolic interchanges of the phosphorylation cycle.

The only experiments with tracer phosphate on muscle permeability which show unequivocally that this membrane can become permeable to phosphate ion are those of Bollman and Flock (23). They occluded the circulation to one extremity for periods up to 4 hr., released the occlusion, and injected tracer phosphate. Under these conditions it could be shown that the muscles which had undergone such drastic treatment did become permeable to phosphate ion.

Kaplan and Greenberg (154, 155) have made extensive studies of the distribution of P^{32} phosphate in liver under a wide variety of conditions. No data are given with respect to the P or P^{32} contents of plasma, and it is therefore difficult to evaluate the data in terms of metabolic interchanges. One fact definitely shown is that the administration of glucose to the fasted rat results in an increase in the ATP content of the liver, and that the phosphate for this is derived from plasma inorganic phosphate rather than from the intracellular inorganic phosphate of the organ.

Lundsgaard (182) has obtained data from perfusion experiments on the livers of cats indicating that the addition of fructose to the perfusing fluid leads to a similar effect. In this species fructose is said to be a glycogen former.

The administration of phlorhizin results in a diminished rate of uptake of P^{32} from plasma phosphate by the liver (155) and kidney (227). These findings may be significant in relation to the hypothesis of Verzar (276) that absorption processes in the intestine, and presumably elsewhere in the body, take place by way of intermediate phosphorylations which are inhibited by phlorhizin.

D. Phosphate compounds in muscle metabolism

Implicit in the formulations given above for the mechanism by which phosphate enters the muscle cell is the assumption that PC and ATP enter into interchanges with other compounds which are essential parts of the metabolic cycle of resting muscle. The exact function of these compounds is still a matter of dispute. Studies of enzyme systems isolated from muscle have led to one formulation, and investigation of the time course of the chemical changes taking place during muscular activity has led to an entirely different one. The use of P^{32} as a tracer in the intact animal has pointed the way to an integration of these apparently opposite formulations. Much remains to be done to complete this synthesis.

The enzyme studies, which have recently been summarized by Potter (225), have led to a concept of interrelated phosphorylation and oxidation reactions, based on ATP as the central point. It is assumed that the same metabolic cycle is operating during contraction as in the resting state. The study of the changes in the phosphate compounds in mammalian muscle contracting *in situ* with normal blood supply has led to the formulation that the energy for contraction is furnished by reactions which do not involve phosphate transfers from and to ATP. The evidence for this view has been summarized by Sacks (241).

Conditions were found under which the injection of tracer phosphate into the anesthetized animal resulted in a differential distribution of the P^{32} among the PC, ATP, and hexosemonophosphate (HMP) (240). Under these conditions, neither a fairly prolonged tetanus under essentially anaerobic conditions (240) nor a long series of twitches under essentially oxidative conditions (242) led to any equalization of the distribution of the P^{32} between these compounds. It follows from this that the reactions which take place during contraction do not involve the phosphate transfers that obviously do take place in resting metabolism, and there is a qualitative separation of the pathways of carbohydrate metabolism in resting and contracting muscle. It may be speculated that the enzyme systems of the activity metabolism are more closely linked to cellular organization than are those of the phosphorylating resting metabolism.

Further evidence for the existence of separate metabolic pathways in resting and activity metabolism is furnished by the observations of Bollman and Flock (22, 77) and Sacks (244) that no increased uptake of phosphate from the plasma takes place during activity, but does occur in a subsequent recovery period.

The tracer experiments on resting metabolism have shown some divergences from the present formulation of the phosphorylation cycle. For example: in cat muscle the tracer experiments show free interchange between fructose-6-phosphate and the PC and ATP, but no interchange between these latter compounds and glucose-6-phophate (244), whereas in frog muscle no interchange was found between the phosphorylated sugars and the PC and ATP (246).

There have been a number of observations with P^{32} showing that the rate of new formation of ATP can be modified in muscle (243, 244, 245) and in liver (154, 155) by the nutritional state of the animal, by the administration of glucose or insulin, or by various enzyme poisons. Some of the data are at variance with current concepts of the phosphorylation cycle. More thorough study on several species may be necessary before the findings on isolated enzyme systems and in the intact animal can be integrated.

E. Mechanism of absorption of glucose

Until the advent of the tracer technique, no clear-cut demonstration had been obtained that the absorption of glucose by the cell involves intermediate phosphorylation reactions. It has been shown (246) that when glucose and tracer phosphate are administered to the fasted cat, there is a temporary accumulation of glucose-6-phosphate on the muscle cell membrane. This effect is absent in the animal in the postabsorptive state (244). The proof that the accumulation of the phosphorylated sugar is on the membrane and not within the cell is that the specific activity of this fraction subsequently falls to a value below that of the PC or ATP. The most satisfactory interpretation of the data is that glucose enters the muscle cell by the formation of the 6-phosphate derivative on the membrane with such a spatial orientation that the glucose portion is directed toward the cell interior and the phosphate portion directed away from the cell. The hydrolysis of the compound then results in the entry of the glucose molecule, while the phosphate remains in the extracellular phase. Application of the same experimental technique to the small intestine and the kidney might determine whether phosphorylation does take place in the absorption of glucose by these organs.

F. Mechanism of insulin action

The use of P^{32} in the intact animal has shown that insulin accelerates the transfer of phosphate across the cell membrane of muscle in the forms of PC and ATP.

This was shown in the fasted cat given glucose by Sacks (245) and in the rat by Goranson (93). The effect is less marked in the cat in the postabsorptive state, because the administration of glucose to such animals depresses the rate of exchange across the membrane (244). Insulin also seems to depress the increased exchange that normally takes place during recovery from muscular activity (245). In traumatic shock, the stimulating effect of insulin on phosphate exchange is not seen (93).

In rabbits given insulin, Kaplan and Greenberg (153) noted an increase in the amount and relative specific activity of the "barium-soluble" fraction of the phosphate compounds of muscle. The data indicate that the largest part of the increase is derived from the PC, but there must also have been some derived directly from plasma phosphate. This fraction consists largely of HMP. The published data are inadequate for an analysis of the process taking place under the influence of insulin, but do indicate species differences. Further application of tracer phosphate to this problem should throw considerable light on both the details of the phosphorylation cycle in the intact muscle cell, and the effects of insulin thereon.

G. Thyroid hormone effects

Greenberg *et al.* (101) have found an increase in the rate of transfer of phosphate across the cell membrane of muscle in hyperthyroid rats, without any effect on the transfer rates in liver and kidney. Conversely, the transfer rate across the muscle cell membrane is decreased in hypothyroidism.

H. Phospholipid metabolism

Although other types of tracer substance have been used in the study of phospholipid metabolism, the ease of use and wide range of applicability of P^{32} have resulted in the abandonment of the other tracers and extensive use of the isotope technique. The simplest application has been to measure the rate of incorporation of P^{32} into the tissue phospholipids following the administration of the tracer as inorganic phosphate (9, 34, 38). A refinement of this consists in obtaining blood plasma from dogs after such treatment, injecting it intravenously into recipient dogs, and following the fate of the labeled phospholipids there present (291). This procedure has given results which are of physiological significance. On the other hand, attempts to isolate such labeled phospholipids from the tissues of animals given P^{32} phosphate and inject them into others have been less successful. The rapid disappearance of such material from the plasma (135) and the distribution of the labeled material among the tissues indicate that it has been treated as foreign particulate matter (122). Very high concentrations were found in the spleen and lung, organs which show low rates of incorporation when P^{32} phosphate is given. Two attempts to trace labeled phosphoric esters, those of ethanolamine (37) and choline (235), failed because the injected substances underwent hydrolysis in the body at fairly rapid rates.

Flock and Bollman (78) found that the glycerophosphate of liver acquired P^{32} from administered inorganic phosphate at a greater rate than did the phospholipids of this organ. This indicates that the esterification of glycerol with phosphate precedes the esterification with fatty acids in the formation of phospholipids. Experiments on slices of kidney and liver (90, 209) have shown that phospholipid formation takes place only under oxidative conditions. It has also been shown (75) that cellular organization is necessary for this synthesis, as it does not take place in homogenates.

A series of experiments by Chaikoff and his collaborators has shown that the phospholipids of plasma are both supplied and removed almost entirely by the liver, although the kidney and small intestine form these compounds at rates only slightly lower than does the liver itself. They found (74) that practically no labeled phospholipid appeared in the plasma of the hepatectomized dog maintained with glucose and given tracer phosphate; the kidney and intestine showed normal rates of phospholipid formation under these conditions. Conversely, the rate of disappearance of injected labeled phospholipid from the plasma, which is normally about 10 per cent per hour (291), is very much less when the liver is excluded from the circulation (64).

The data of Bollman and Flock (24) indicate that in the rat about one-fourth of the total amount of phospholipid formed in the liver is transferred to the plasma. These data, together with the observation that the turnover rate of intestinal phospholipid is higher in animals on a high fat diet than on a high carbohydrate diet (10), and the further finding (222) that administration of fat increases the rate of formation of phospholipid by the intestine, are consistent with the hypothesis that phosphorylating reactions are involved in fat transport and metabolism. However, Bollman and Flock calculated from their data that the total amount of phospholipid formed in the liver was adequate to account for only about 3 per cent of the fat undergoing transport in the course of metabolism. This would seem to exclude the possibility that phosphorylation is an obligate stage in fat transport.

Studies by means of injection of plasma containing labeled phospholipids (234) indicate that these substances pass directly from plasma to intestinal lymphatics. The major portion of the phospholipids present in thoracic duct lymph, however, are synthesized by the intestine, with a smaller portion arising in the liver (79). The greatest part of the increased phospholipid content of thoracic duct lymph which appears after feeding fat was found to arise in the intestine also (79). The inflow from the liver was increased somewhat by feeding fat.

In the adrenalectomized rat, Stillman *et al.* (262) found normal rates of formation of phospholipid in the intestine, irrespective of whether the animals were suffering from untreated cortical insufficiency or were maintained by the administration of sodium chloride. These observations, together with those of Bollman and Flock (24) on the quantitative unimportance of phosphorylation in fat transport, would seem to dispose of the hypothesis of Verzar that the decreased intestinal absorption of fat in adrenal insufficiency is due to impairment of the phosphorylating mechanism.

The time course of the uptake of P^{32} by the phospholipids of muscle, when the tracer is administered as inorganic phosphate, does not permit an answer to the question of whether the phospholipids are formed there or merely transported to muscle by the plasma. This follows because the rate of appearance of the P^{32} in muscle phospholipids is low in comparison to the rates for liver and plasma (9, 38). Indirect evidence, obtained from the intravenous injection of plasma containing labeled phospholipid (291), shows that the musculature accounts for an appreciable fraction of the phospholipid removed from the plasma, and denervated muscle shows a higher uptake than normal muscle (6, 87). These findings would seem to indicate that the phospholipids present in muscle are acquired by transport rather than by synthesis *in situ.*

Treatment of the rooster with the synthetic estrogen diethylstilbestrol results in a marked increase in the rate of formation of phopsholipids by the liver and in the amount of phospholipid transferred to plasma by the liver (78). The removal of phospholipid from plasma by the liver is increased slightly by this treatment of the animal. The increased rate of formation of phospholipids has also been shown (268) in slice experiments using livers of estrogen-treated roosters.

Experiments with P^{32} phosphate by Hevesy and L. Hahn (133), by Chargaff (35), and especially by Lorenz *et al.* (180) have shown that phospholipids once incorporated into the growing egg yolk in the hen do not undergo any subsequent breakdown reaction which releases phosphate or phospholipid to the plasma. Lorenz *et al.* also showed that the phosphoproteins of the white are formed in the early stages of growth of the yolk, ready for deposition around the yolk at the time the yolk is fully grown. Hevesy *et al.* (136) injected P^{32} phosphate into the egg, and after incubation found that the tracer was present in the phospholipids of the embryo but not in those of the yolk. This demonstrates that the phospholipids of the yolk were not transported as such to the embryo.

Radiophosphorus has been used extensively in the study of lipotropic effects of choline and other compounds, but in many of the earlier papers describing such studies, the experimental data were incomplete, and therefore do not establish any necessary connection between lipotropic activity and phospholipid turnover. The theoretical basis for such connection implies phospholipid formation as an obligate stage in fat transport. The early reports (220) that choline increased the P^{32} content of the liver phospholipids in rats with fatty livers included no determinations of lipid or phospholipid content of the liver, and hence are not of critical value. More recent experiments by Horning and Eckstein (143) indicate that the increased P^{32} content of the liver which results from the administration of choline or methionine in such animals can be accounted for by an increase in the phospholipid content of the organ, which is not always accompanied by a fall in total lipid content. These authors state that there may be no relation between this phospholipid effect and lipotropic action. Artom and Cornatzer (7,8) conclude, from their experiments on animals on a low-fat, low-protein diet, that the effect of choline is to stimulate phospholipid formation, rather than to accelerate the turnover. Both methionine and cystine have been found (222) to increase the uptake of P^{32} by the phospholipids in the liver of animals on a diet producing fatty livers. Methionine has a lipotropic action, but cystine has the opposite effect. It is therefore difficult to relate the observed effect to lipotropic activity.

Bollman and Flock (24) have made a very thorough study of phospholipid turnover in the liver. By proper design of experiment, following the relative specific activity of plasma and liver inorganic phosphate as well as that of liver phospholipids, they have established that the rate of formation of liver phospholipids in the rat is remarkably constant. Their data have been calculated in terms of phospholipid phosphorus formed per hour per 100 g. of body weight. Changes in composition of diet which influence the size and phospholipid content of the liver were found to be without effect on the rate of formation of phospholipid in this organ, in the terms given above. Partial hepatectomy was found to increase the rate of formation per gram of liver and carbon tetrachloride injury, which gives livers of increased size, resulted in decreased formation rate per gram of liver tissue, but in both cases there was no departure from the normal rate of formation of liver phospholipid per 100 g. of body weight of animal. An effect of choline on turnover rate could be demonstrated in the fatty livers resulting from a choline-free diet, but not in animals whose diet contained adequate choline to prevent the formation of fatty livers.

The turnover rate of lecithin was found to be higher than that of cephalin both in normal tissues (38, 134) and in tumors (121). It has also been reported that choline administration increases the turnover rate of the choline-containing phospholipids of liver (63) and of plasma (187), without affecting the turnover rate of the non-choline-containing phospholipids. The dose of choline chloride used, 300 mg. per kilogram, is so high that the observed effect may be a mass-action one rather than one of physiological significance.

I. Nucleic acid metabolism

The data obtained on the time course of the uptake of P^{32} by these compounds indicates that the ribosenucleic acids of cytoplasm undergo metabolic turnover, while the new formation of desoxyribosenucleic acids in cell nuclei represents primarily growth rather than metabolic turnover. This is indicated by the relatively rapid uptake of P^{32} by the desoxyribosenucleic acids of liver and spleen of rats 3 to 4 days old, as compared to the slow uptake in adult animals (1). Also, Brues *et al.* (29) found rather close parallels between the uptake of P^{32} by the desoxyribosenucleic acids and the mitotic activity, both in liver regenerating after partial hepatectomy and in the tumor Hepatoma 31. In adult animals, Ottesen and his collaborators (3, 139) found the highest uptake rates in those tissues in which new cells are formed throughout the life of the animal: bone marrow, mucosa of the small intestine, etc. Radiation with x-rays produces an immediate decrease in the rate of incorporation of P^{32} into desoxyribosenucleic acids, but the rate returns rapidly to normal. The effect was seen both in normal tissues (1) and in tumors (65, 66). On the other hand, Marshak (191) reported that x-radiation led to decreased uptake of tracer phosphate by the cytoplasm and increased uptake by cell nuclei.

Marshak and Walker (193) have used P^{32} in a very ingenious experiment on chromatin. They injected tracer phosphate in rats, and after some time isolated from the livers, chromatin strands which contained the tracer. When suspensions of these chromatin strands were injected intravenously into rats which had previously undergone partial hepatectomy, the P^{32} uptake by the liver was several times as high as when the tracer was injected as inorganic phosphate or ATP. The result found may represent either the incorporation of intact chromatin into regenerating liver cells, or the engulfment of the chromatin strands as foreign particles by the reticuloendothelial cells of the liver. If the former be the case, it represents the only reported instance in which a labeled organic phosphate compound not normally found in plasma escaped hydrolysis after injection. Labeled nucleic acids from liver, obtained by a similar technique, were found to undergo rapid hydrolysis after intravenous injection or on incubation with liver slices (2).

J. Other applications of P^{32}

Lindsay and Craig (176) used the radioautograph technique to study the distribution of phosphate in various stages of development of a number of insect species. Born *et al.* (25) and Stanley (261) attempted without success to obtain differential distribution of this tracer between tobacco mosaic virus and the host plant, by adding tracer phosphate to the nutrient solution in which the young plants were growing. In plant materials a non-metabolic uptake of P^{32} phosphate from nutrient solution has been demonstrated (27, 130, 217). It has also been shown (27) that light and favorable environmental temperatures increase the metabolic uptake of phosphate by plants. Biddulph (21) and Arnon *et al.* (5) were able to show shifts of phosphate taking place between plant roots and leaves and from leaves to fruit. Stout and Hoagland (263) showed by the following experiment that migration of phosphate in woody plants takes place only through the wood and not the bark. They separated bark and wood for a short space by inserting waxed paper, then added tracer phosphate to the nutrient solution. After some time, relatively high concentrations of P^{32} were found in the bark above and below the separated portion, but practically none in the separated portion itself.

V. SULFUR

Most of the tracer experiments with this element involve the synthesis of labeled cystine or methionine, by methods capable of giving the greatest possible conversion of sulfur to the desired compound. The relatively long half-life, 87 days, allows adequate time for the carrying out of the synthetic reactions and even rather prolonged animal experiments. On the other hand, the low energy of disintegration of S^{35} requires special methods for measurement of the radiation.

Two experiments with this tracer point out the necessity for caution in translating the results of *in vitro* experiments into terms of metabolic reactions taking place in the intact animal. One of these concerns the formation of cystine from pyruvate, ammonia, and sulfide sulfur by an enzyme present in liver. Smythe and Holliday (259) used sulfide containing S^{35} to demonstrate that the reaction does involve the incorporation of sulfur present in this form into the cystine formed. However, Dziewiatkowski (60) was able to show that in the intact rat only a very small fraction of the cystine present in hair, skin, muscle, or the liver itself could have come from this reaction. Even when the formation of cystine was promoted by feeding bromobenzene, this possible mechanism of synthesis had little quantitative significance.

The other illustration comes from the experiments of Melchior and Tarver (196) on the incubation of S^{35} cystine with homogenates of liver. Under these conditions, a rather rapid incorporation of cystine into the proteins took place. It was shown to be present there through sulfhydryl linkages and not by peptide bonds. When S^{35} methionine, which has the sulfhydryl group blocked, was used, none of the amino acid was incorporated into the proteins of the homogenate.

The biological conversion of methionine to cystine has been shown in the intact animal by Tarver and Schmidt (265) and in liver slices by Melchior and Tarver (196), by the use of methionine containing S^{35}. Tarver and Schmidt (266) also showed by this means that the taurine of the bile may arise from methionine.

The mechanism postulated by Tarver and Schmidt for the conversion is the following: demethylation of the methionine to homocysteine, migration of the sulfhydryl group from the gamma to the beta carbon, and demethylation of the resulting β-methylcysteine. However, du Vigneaud *et al.* (277) were able to show, by the use of doubly labeled methionine, that this postulated mechanism is not the one used by the body. They prepared methionine with excess C^{13} in the β- and γ-positions and excess S^{34}. This was fed to rats; after some time the hair was clipped, and from it the cystine was isolated. It contained excess S^{34}, but no excess C^{13}, and therefore the carbon chain of the methionine was not used in the cystine formation. du Vigneaud *et al.* discuss a number of other possible mechanims for this conversion which have been postulated at various times.

Radiosulfur has been used to throw more light on the origin of the plasma proteins than was possible to obtain from ordinary experimental methods. There is overwhelming evidence that the liver is the site of formation of most of these, and its contribution is so great as to mask other possible sources when ordinary techniques are used. However, Tarver and Reinhardt (264) have recently shown, by the use of S^{35} methionine in the hepatectomized animal, that an appreciable fraction of the globulins and a smaller fraction of the albumin of plasma have an extrahepatic origin. Their results indicate that fibrinogen is formed exclusively by the liver. They have also been able to demonstrate by this means that other tissues than the liver, in particular the intestinal mucosa, can convert methionine to cystine.

Mention should also be made of the ingeniously planned but only partly successful attempts of Seligman and Fine (254) to obtain plasma proteins labeled with S^{35}. They synthesized cystine, homocystine, and methionine with S^{35} and fed these, together with casein, to dogs which had been rendered hypoproteinemic by plasmapheresis. After a few days there was obtained from these animals plasma which did contain some S^{35} in protein combination. The yields were too low to be practical for use in their program of studying changes in capillary permeability in traumatic shock. They were able to carry out a few experiments in which the rate of disappearance of the labeling agent from the plasma was followed in dogs which had been injected intravenously with the labeled plasma proteins. The rate of disappearance found (72) indicates a turnover rate of about 1.5 per cent per hour for the plasma proteins.

VI. CALCIUM AND STRONTIUM

The only radioactive isotope of calcium that has a half-life long enough to permit its use in biological tracer experiments is Ca^{45}. The energy of disintegration of this radioelement is so low that measurements on it can be made only with great losses due to self-absorption, scattering in air, and absorption by the window of the Geiger counter tube. It has therefore not been used to any great extent. Instead, a number of experiments have been carried out with Sr^{89} as a substitute tracer. This isotope has both a favorable half-life and high energy of disintegration.

The findings have been that radiostrontium is only a qualitative, and not a quantitative, substitute for radiocalcium in tracer experiments, both in plant (257) and in animal (218) material. A survey of the data obtained in many of the experiments raises serious questions about the effectiveness of this substitute tracer. Most of the information obtained would appear to have been as readily obtainable by ordinary methods of investigation.

Studies on calcium metabolism and transport in pregnancy and lactation (219), in rickets (97, 280), and in the healing of fractures (49, 192) are among those which have been made with these radioelements.

VII. IRON

Studies on the metabolism of iron have been concerned principally with the factors influencing absorption from the gastrointestinal tract, storage in the tissues, and conversion to hemoglobin. Decades of research by ordinary experimental methods have yielded an extensive literature characterized by controversy and confusion. A few years of experimentation with radioiron have led to a clearly defined picture. By this means it has been established beyond a reasonable doubt that the principal factor which determines the absorption of iron from the gastrointestinal tract is the need of the body for iron for the formation of the hemoglobin of the red cell. The mechanism by which this need is made effective remains to be found.

The key to the problem was given by the experiments of P.F. Hahn, Bale, Lawrence, and Whipple (107). They fed Fe^{59} as ferric sulfate to normal dogs and to others rendered anemic by low-iron diet plus repeated bleedings. Only traces of iron appeared in the blood of the normal animals, but prompt absorption of a rather large percentage of the tracer took place in the anemic animals. It appeared in the plasma within a few hours; by 24 hr. the iron had practically disappeared from the plasma and was present in large amount in the circulating red cells. The concentration in the red cells increased for several days following the administration of a single dose of labeled iron. Since no exchange reaction took place between plasma and corpuscle iron (108), the data must signify transport by the plasma to the bone marrow and incorporation there into newly forming red cells. Some details have been added by further study, but the essential results have been fully confirmed by subsequent experiments. For example, Austoni and Greenberg (12) found that relatively more iron is absorbed by normal rats than Hahn *et al.* noted in normal dogs. They also observed greater differences in absorption of iron between normal and anemic rats than had been found in dogs. Copp and Greenberg (50, 51) used Fe^{55} preparations of relatively high specific activity to show that anemic rats might absorb up to 90 per cent of a single 50-γ dose of iron.

So well established is this difference in absorption of iron between the anemic and normal, that radioiron is being used clinically as a test for iron-deficiency anemia (203). A normal individual may absorb 1 or 2 per cent of a dose of 2 mg. per kilogram, whereas the anemic subject may absorb as much as 50 per cent of such a dose. In pregnancy, the amount absorbed may be as much as ten times the normal, even in cases which show no hematologic evidence of iron deficiency (13).

Absorption of iron appears to take place from the stomach as well as from the intestine. P. F. Hahn *et al.* (110) demonstrated active absorption from pouches of the stomach, duodenum, and jejunum in dogs, and Copp and Greenberg (50) found evidence in rats that absorption of iron also takes place from the colon.

In anemic human subjects, both P. F. Hahn *et al.* (114) and Moore *et al.* (203) found greater percentage absorption of ferrous iron than of ferric, and Hahn *et al.* found the same situation in anemic dogs. Moore *et al.* found such a preferential absorption of ferrous iron in only some of their anemic dogs. Both groups are in agreement that the anemic human subject shows a similar preferential absorption of ferrous iron, and Moore *et al.* found it in their normal male subjects also.

The mechanism for the absorption of iron may be "saturated". This was shown by P. F. Hahn *et al.* (110) by administering a dose of an ordinary iron salt by mouth to anemic dogs 1 to 6 hr. before feeding a tracer dose. Under these conditions, the percentage absorption of the tracer dose was considerably less than anticipated.

Little storage of orally administered iron takes place in the liver or other organs (51). Rather high concentrations are found in the bone marrow during the first several hours after oral administration, but most of this disappears in a day or two, especially in anemic animals. Transport of iron from mother to fetus takes place principally through the plasma: Pommerenke *et al.* (224) gave radioiron salts by mouth to pregnant women shortly before anticipated delivery. In the three cases in which the birth of the child took place within 2 hr. after giving the tracer, the Fe^{59} content of umbilical vein plasma was very close to that of maternal plasma taken at the moment of delivery.

The utilization of intravenously injected iron for red cell formation takes place fairly promptly and completely in normal dogs (58) under conditions in which orally administered iron would not be absorbed. This finding is considered as evidence that there is a preferential utilization of recently stored iron for hemoglobin formation over that which had previously been stored in the tissues.

The immediate fate of ferric iron injected intraperitoneally is quite different from that of orally administered iron. Copp and Greenberg (51) found in rats that a large portion of the injected dose appeared in the liver within a few hours, and that it was released to the marrow only over a period of several days. Some storage of the injected iron was found in the spleen. The administration of a copper salt together with the iron salt was found to reduce the storage in the liver quite markedly, even though the animals were not showing any signs of copper deficiency.

The principal storage form of iron in the liver, spleen, and bone marrow is the complex of protein and colloidal ferric hydroxide, ferritin (96). Granick and his collaborators (95, 113) have shown, by the use of Fe^{59}, that the liver rapidly converts the major portion of a dose of ferric salt, given intravenously, into this complex within a very few hours, even though large amounts are already present within the organ. The iron liberated from the destruction of red cells was also found to be stored in this form, principally in the liver and to a lesser extent in the spleen.

Copp and Greenberg (51), working with rats, and P. F. Hahn *et al.* (109), using dogs, found that practically no iron is excreted by the body. The iron liberated from the normal destruction of red cells is retained and utilized for the hemoglobin of newly forming ones. Of the iron liberated by normal red cell destruction, only about 3 per cent is excreted in the bile (124) and this is absorbed again by the intestine. For this reason, it is not possible to use this tracer to determine the average life of the red cells. Even when excessive red cell destruction is caused, for example, by the action of acetylphenylhydrazine (55), the iron is re-utilized completely.

The fate of intraperitoneally injected red cells has been studied by P. F. Hahn *et al.* (115) by injecting tracer iron in anemic dogs, and after several days injecting blood from them into recipient animals. In some instances the labeled cells were found in the circulating blood within a few hours; in others, the appearance of Fe^{59} in the circulation was delayed for several days, indicating that the injected cells had first been destroyed and their iron used to form new ones. It is quite likely that these cases of delayed appearance of the tracer in the blood of the recipient dog represent transfusion incompatibilities.

The only exception to the general rule that iron is absorbed from the gastrointestinal tract when needed for hemoglobin formation is in the case of inflammatory reactions. In chronic infections accompanied by microcytic anemia (13) and in the presence of an acute sterile abscess produced by the injection of a turpentine emulsion in anemic dogs (111), there is failure to absorb orally administered iron. In febrile conditions, even intravenously injected iron is utilized only very slowly and incompletely for hemoglobin formation, even when an iron deficiency anemia is present (58).

VIII. BROMINE

The use of radiobromine in studies on diffusion and permeability has been discussed in Section III. A somewhat related case is the demonstration by Perlman *et al.* (222) that the thyroid gland concentrates bromide in the same way that it concentrates iodide, and that in the hyperplastic state produced by thyrotropic hormone the capacity of the gland to concentrate bromide is increased in the same manner as the capacity to concentrate iodide.

Most of the tracer uses of radiobromine have been in the nature of a substitute tracer, either for chlorine or for labeling some organic compound which could not otherwise be readily prepared with a radioelement. For example, Hansen *et al.* (117) prepared monobromobenzene containing Br^{82}, and condensed this with chloral to give a dibromo analog of DDT. This compound, which is only slightly inferior to DDT as an insecticide, was used to kill susceptible insects, and the distribution in the insects determined by the radioautograph technique. The half-life of Br^{82} is 34 hr., whereas that of Cl^{38} is only 37 min.; hence the experiment with the chlorine derivative would not be feasible.

As illustrations of the use of radiobromine as a substituent to make an organic compound traceable, the preparation of brominated Trypan Blue and Evans Blue (205, 206) and of the dibromo derivative of 1-amino-8-naphthol-3,6-disulfonic acid (159) may be cited. These dyes were used to study the capillary permeability to colloids that takes place in sites of acute inflammatory processes. The γ-rays from the disintegration permit determinations of relative concentration of the dye in different areas of the body, by placing the proper type of Geiger tube over the area. It was found possible to localize inflammatory lesions in the extremities by this means, but the method failed when applied to deep lesions. It was also found by this means that tumors do not concentrate these colloidal dyes to any abnormal extent, indicating that the capillaries in the tumors do not have qualitatively abnormal permeability (206).

Fine and Seligman (72) brominated plasma proteins with radiobromine to study the question of plasma leakage in shock. They were able to obtain preparations in which up to 97 per cent of the bromine present was in protein combination. These bromoproteins disappeared more rapidly from the blood stream than did the labeled proteins obtained by feeding S^{35} amino acids to dogs (254). The rate of disappearance of the brominated proteins was roughly proportional to their bromine content, indicating that they were treated as foreign substances. Attempts to calculate the turnover rate of plasma proteins from the use of such labeled material would give erroneously high values.

The one instance in which a compound containing radiobromine has been used in relation to its action in the body is that of the synthetic estrogen α-bromotriphenylethylene. Daudel *et al.* (56) used Br^{82} in the synthesis of this compound, and studied its distribution in the tissues of the mouse. The highest concentration was found in the ovary, and in this organ was reached in about 15 hr. The concentration in the uterus was not as high as in the ovary, but was reached within 3 or 4 hr. after injection, and remained at the peak level for the

30 hr. over which observations were made. The estrus response appeared about 48 hr. after injection, as was to be expected.

IX. IODINE

An ingenious application of radioiodine as a tracer has been made by Reiner (231, 233), based on his discovery (232) that insulin can be coupled with aromatic diazo compounds under certain conditions and retain its physiological activity. *p*-Iodoaniline was made with radioiodine, diazotized, and coupled with insulin. The resulting product was injected subcutaneously, and the rate of absorption from the injection site followed by placing a γ-ray-sensitive Geiger counter tube over the injection site. The absorption of ordinary insulin was found to be proportional to the logarithm of the amount remaining, up to about 80 per cent disappearance from the injection site, indicating absorption by simple diffusion. With protamine zinc insulin and globin insulin, however, the absorption process was found to be considerably more complex.

Experiments such as this illustrate the value of the tracer technique in certain cases which could not otherwise be subjected to experimental investigation, and at the same time point out the necessity for extreme caution in the interpretation of such data. The question arises, at what point in the metabolism of the tracer compound did a separation of the aromatic group containing the tracer from the rest of the molecule take place? There is no way of ascertaining whether the diazo group was reduced in the process of absorption or only after the azo insulin had been transported to the liver. Also, the question must remain unanswered as to whether it was the azo insulin or the regenerated insulin which was physiologically active.

The great interest in tracer applications of iodine has naturally been in the study of thyroid physiology. The first such application was made by Hertz and his coworkers (128). They showed that in the normal rabbit there is an extremely marked concentration of intravenously injected iodide by the thyroid within a few minutes after injection. In animals with thyroids made hyperplastic by a cabbage diet or the injection of thyrotropic hormone, there is an even greater concentration of the iodide by the gland. The fundamental observations of Hertz *et al.* have been confirmed in a number of species (4, 163, 172, 173, 210), and have also been shown in slices of thyroid tissue by the Warburg technique (248).

The greatest part of the experiments has been in the study of the effect of alterations in the state of thyroid function on the capacity of the gland to concentrate iodide, and to convert it to diiodotyrosine and thyroxine. With the development of antithyroid substances of the type of thiouracil (11), the emphasis of the tracer studies has shifted to attempts at elucidation of the mode of action of these substances.

Conditions which increase the functional activity of the thyroid bring about an increase in the capacity of the gland to concentrate iodide, and decreased functional activity diminishes the concentrating capacity. For example, exposure of rats to a cold environment increases and exposure to a warm environment decreases the iodine-collecting capacity of the gland (167). These changes are noted only during the period before adaptation to the new environmental temperature takes place. Treatment with thyrotropic hormone, as might be expected, increases the iodine-collecting capacity of the thyroid (127, 128, 156, 171, 210). Hypophysectomy reduces, but does not abolish completely, the iodine-collecting capacity of the thyroid (170, 172, 210). It is stated that the thyroid of the hypophysectomized animal is unable to convert diiodotyrosine to thyroxine (210).

When iodide is administered to animals which have previously been on a diet deficient in iodine, there is a marked acceleration in the rate of iodine uptake by the thyroid (168). The percentage uptake of the administered dose increases with dose up to a certain point; beyond this the absolute amount taken up continues to rise, although the per cent of total dose collected may show a decrease (172). When the tracer iodine was present as iodate or diiodotyrosine, the collection by the thyroid showed a lag, indicating that these were probably converted to iodide before fixation (172). Even when labeled thyroxine was injected into rabbits, some of the iodine was found fixed in the thyroid as inorganic iodide (147).

Experiments with thyroid slices (247, 248) have shown that fixation of iodine takes place only when the cytochrome system is operating. However, concentrations of azide which inhibit the cytochrome system were found by the same investigators not to affect significantly the uptake of iodine in the way that cyanide and sulfide did.

The initial fixation of inorganic iodide by the thyroid is followed by fairly rapid conversion to organic forms. Lein (173) found more organically bound iodine present in the gland 12 hr. after the administration of the tracer than had been initially fixed as iodide. Leblond *et al.* (169) showed by a combination of chemical and histological techniques that the principal storage form is diiodotyrosine. Chagas *et al.* (33) have followed the time course of the accumulation of tracer iodide in the colloid by a micromanipulation technique which permitted the aspiration of the contents of single follicles. Leblond (165, 166) used histological and radioautographic techniques together, to show that acidophilic colloid contains higher concentrations of tracer iodine than does basophilic colloid. Since it is generally considered that the basophilic colloid represents a more active state, Leblond interpreted his findings to mean that the lower concentration signified a more rapid secretion of thyroid hormone into the blood stream from the basophilic colloid.

In the normal dog, Mann *et al.* (190) calculated from the time course of tracer iodine content of the thyroid, that the gland forms about 1.5 per cent of its thyroxine content per hour.

Joliot *et al.* (147) report that the thyroid collects a much smaller fraction of a dose of tracer iodine when this is administered as thyroxine than when it is given in inorganic form, and also that the urinary excretion of the tracer is much greater in the former case. These workers also found (148) that several days' treatment of an animal with thyroxine resulted in a "resting state" of the thyroid during which there was a greatly reduced uptake of a tracer dose of iodide. These observations are hardly to be expected from what is known of the duration of action of a single dose of thyroxine, and it is difficult to see how a substance which is rapidly excreted can bring about a resting state in the thyroid.

In the fetal rat, Gorbman and Evans (94) report that the capacity of the thyroid to collect iodine is first noted on the nineteenth day of the 22-day gestation period, at the same time that colloid follicles make their appearance.

Studies on thyroid slices by Chaikoff and his collaborators (208, 209) have shown that the conversion of iodide to diiodotyrosine and thyroxine is a function of cellular organization, as it does not take place in homogenates. These workers also noted that high concentrations of iodide in the medium in which the slices are suspended tend to inhibit the conversion reactions.

Morton *et al.* (211) report that in the thyroid made hyperplastic by thyrotropic hormone treatment, there is both an acclerated conversion of iodide to diiodotyrosine and thyroxine and an accelerated rate of secretion of thyroxine by the gland. Keating *et al.* (156) were able to show the latter effect in chicks after a single dose of thyrotropic hormone. It should be pointed out that this accelerated loss of iodine from the thyroid under the influence of thyrotropic hormone had been demonstrated by Schockaert and Foster (250) by ordinary analytical methods.

The thyroid hyperplasia caused by goitrogenic substances such as thiouracil has been studied extensively with radioiodine. On the basis of such studies, the goitrogens can be separated into those which decrease the iodine-collecting capacity of the thyroid and those which increase it. Most of the clinically used compounds, such as thiouracil and its homologues, and thiourea, are in the former group (52, 53, 84, 157, 162, 163, 228, 230). On the other hand, in the hyperplasia resulting from the administration of acetonitrile or thiocyanate, the iodine-collecting capacity of the thyroid is markedly increased (128, 228), but the capacity to convert the iodide into diiodotyrosine is blocked (230, 251). Still other substances, such as 1-aminothiazole, which is used clinically in France, appear to block the conversion reaction without affecting the capacity of the gland to collect iodine (147). To complicate the situation still further, some antithyroid compounds have been found (228) to result in decreased iodine-collecting capacity in rats and increased capacity in chicks.

The data referred to above have all been gained from chronic administration of the antithyroid substance to the experimental animal. Rawson *et al.* (228) have reported preliminary observations which indicate that a single dose of practically any of the goitrogens has a similar effect over a brief period during which it is present in effective concentration. Experiments on thyroid slices by Chaikoff and his collaborators have given results which are not altogether in harmony with the data obtained on the intact animal. They found (82, 83) that thiouracil, thiourea, *p*-aminobenzoic acid, and the sulfonamides do not affect the uptake of tracer iodide by the slices, but depress the conversion to diiodotyrosine. Acetonitrile was found to be without effect on either the uptake or the conversion, and thiocyanate to inhibit the uptake of the tracer. They also state (267) that of the compounds they tested, every one which Astwood (11) had reported to be effective as a goitrogen in the intact animal was able to inhibit the conversion reaction.

No completely satisfactory theory has yet been offered for the mechanism of this goitrogenic or antithyroid action, or for the beneficial effect this clsas of substances has on clinical hyperthyroidism. A full account of this subject would be beyond the scope of this review. The facts that have been established by the use of tracer iodine in this disease do call for mention. There is general agreement (116, 118, 129) that in the clinical condition there is an increased uptake of tracer iodine by the thyroid and an increased rate of secretion of thyroid hormone into the circulation. Accompanying this, the urinary excretion of the tracer dose is diminished (229). When thiouracil or some similar compound is administered and the symptoms of hyperthyroidism are reduced, the urinary excretion of a test dose of tracer iodide is raised to the normal level (116), and presumably the fixation by the thyroid is reduced to a corresponding degree.

X. MISCELLANEOUS ELEMENTS

Included in this section are the heavy metals and the metalloids. Radioactive isotopes are particularly valuable in the study of the distribution and excretion of such trace elements, which are present in the tissues in such minute amounts that ordinary chemical methods are unsatisfactory for their quantitative estimation. Kurbatov and Pool (160) have presented a theoretical discussion of the principles involved in the use of radioactive isotopes of trace elements for metabolic studies.

Among the studies which have been made by this means are: those on manganese by Greenberg *et al.* (100) and Mohamed and Greenberg (199); on cobalt by Copp and Greenberg (48), Comar *et al.* (43), and Sheline *et al.* (256); on zinc by Montgomery *et al.* (201) and Sheline *et al.* (255); on selenium by McConnell (194, 195); and on gold by Ely (62).

Distribution and excretion studies have been made with radiocopper in connection with its function in erythropoiesis. Yoshikawa *et al.* (290) found that it appeared in the plasma within a few hours after oral administration, but was not present in the circulating red cells until after the plasma content declined below the peak value. Schultze and Simmons (251) found a greater percentage retention of an orally administered dose in animals which had been on a copper-deficient diet than in those with dietary iron deficiency. The highest concentrations were found in the liver, kidney, and bone marrow. The latter probably represents concentration in connection with the function in red cell maturation.

The distribution and excretion of arsenite has been studied by Hunter *et al.* (144) and Lowry *et al.* (181); that of arsenate has been studied by Du Pont *et al.* (59). Lawton *et al.* (164) have made some preliminary observations on an experimental approach to the mechanism of the chemotherapeutic effect of arsenicals in experimental filariasis, by demonstrating that injected arsenic compounds were concentrated to a relatively great extent by the parasites within the infested animal. A higher concentration of the arsenic was found in the parasites than in any tissues of the host other than the liver and kidney. In this connection, it should be noted that Hawking (123) demonstrated by ordinary experimental techniques that susceptible strains of trypanosomes concentrate therapeutically active arsenicals, whereas resistant strains do not. The compounds used by Lawton *et al.* are not therapeutically active. Similar studies with active compounds containing radioarsenic may yield useful information on relative host-parasite concentrations.

Brady *et al.* (26) have used radioantimony in the same manner as was done for radioarsenic by Lawton *et al.*, to show that filaria in a host animal show a concentration of this element.

The natural radium D isotope of lead was used by Mortensen and Kellogg (207) to study the uptake of lead by the erythrocyte *in vivo* and *in vitro*. In dogs they found that doses of lead up to 1 mg. per 100 cc. of blood were completely taken up by the red cells within 10 to 15 min. after intravenous injection. *In vitro*, the process was found to have the characteristics of a first-order reaction.

In this connection it should be pointed out that the very first biological tracer application of a radioactive isotope was the study by Hevesy (131) in 1923 of the uptake of radium D by plants. Hevesy was also the first to use artificially produced radioactive isotopes as tracers in biology (39).

Even the radioactive isotopes of the rare gases have been used as tracers. Cook and Sears (45) attempted to use radiokrypton to study the mechanism of bends. They found that agents which altered blood pressure, blood flow, or capillary tone modified the time course of the concentration of the gas in the peripheral tissues in the anticipated direction. The magnitude of the changes found was not great, and the possible value of this investigation must await similar studies with other inert gases.

Other unusual instances of tracer applications include the preparation by Hamilton and Soley (117) of the hitherto unknown element 85 as a radioactive isotope, and the study of its uptake by the thyroid. The physical properties of the element are those of a heavy metal rather than of a halogen, yet it is taken up selectively by the thyroid, and treatment of the animals with thyrotropic hormone increases the relative uptake by the gland in a manner qualitatively similar to the effect on iodine uptake.

Recently Van Middlesworth *et al.* (272) reported preliminary observations on the time course of the uptake of radioactive strontium, yttrium, and plutonium in the callus of healing fractures. They injected all three isotopes simultaneously in the same animal, and were able to make determinations of all three in the same tissue samples, because the radiations are respectively pure β, γ, and α. The uptake of strontium was found to be associated with calcification, but the other two elements are concentrated in the site of fracture several days before the onset of calcification.

XI. TRACER STUDIES ON SHOCK

A number of radioelements have been used in studies to determine whether the capillary dilation that is present in shock is accompanied by a qualitative change in the permeability of the capillaries. The data obtained from the use of Na^{24}, P^{32}, S^{35}, Fe^{59}, Br^{82}, and I^{131} are in rather general agreement and will be discussed together.

P. F. Hahn *et al.* (109, 112) found by the use of red cells labeled with Fe^{59} that the immediate rise in plasma volume which follows hemorrhage restores the total blood volume, and that as red cells are regenerated there is a corresponding decrease in plasma volume. They were also able to show that no appreciable sequestration of transfused red cells takes place in the spleen or bone marrow. However, the administration of pentobarbital was found (106) to lead to the sequestration of up to 30 per cent of the total circulating red cell mass in the spleen of the dog. Injection of epinephrine brought about contraction of the spleen and return of the red cells to the circulation.

This effect of pentobarbital, and presumably of other barbiturates, may explain why Seeley, Essex, and Mann (253) found that there was a delay in the onset of shock from manipulation of the intestines in animals under barbiturate anesthesia, in comparison with those under ether. The increase in plasma volume under barbiturates, consequent upon the removal of the red cell mass by the spleen, may have enabled a greater loss of fluid into the dilated capillaries to take place before critical degrees of hemoconcentration developed than would be the case under ether anesthesia.

Gellhorn *et al.* (92) found that the total rate of transfer of Na^{24} across the capillary membrane was reduced in shock to about half the normal value. This can readily be accounted for by the reduction in cardiac output, without reference to altered capillary permeability. Fox and Keston (81) found that, in burn or tourniquet shock in mice, about half of the extracellular sodium ion became unavailable to the circulatory system; by the use of Na^{24} they showed that the cell membranes of the tissues became permeable to this ion only in those structures which had undergone the trauma.

Bollman and Flock (23) performed similar experiments with P^{32} phosphate in rats, and arrived at a similar conclusion. They occluded the circulation to one limb for periods up to 3 hr., released the tourniquet, and then injected tracer phosphate intravenously. The distribution of the P^{32} found 1 hr. later indicated that the membranes of the traumatized muscle, and only this tissue, had become permeable to phosphate ion. At the same time the plasma inorganic phosphate showed a marked rise, indicating passage of this ion from the traumatized muscles to the extracellular phase. No evidence was found that PC or ATP diffused out of the muscles.

Seligman and Fine (254) attempted to use plasma proteins containing S^{35} to determine whether there was any loss of plasma as such to the extracellular fluid in shock. They synthesized cystine, homocystine, and methionine containing S^{35}, fed these along with casein to dogs with low plasma proteins, and some days later took plasma from these dogs for transfusion into normal recipient dogs. The over-all conversion of the fed amino acids to plasma proteins was so poor that they were unable to use this labeling agent effectively. They turned first to Br^{82} (71, 72) and then to I^{131} (71, 73) as a means of labeling the plasma proteins, by treating them with these halogens. The rate of disappearance of these halogenated proteins from the plasma of recipient dogs was roughly proportional to their halogen content. Comparison of the rate of disappearance in normal dogs and in dogs in shock indicated that there was no leakage of proteins from the plasma into the tissues generally. Only in the traumatized tissues did the capillaries become permeable to plasma proteins.

Fine and Seligman were also able to show (71), by means of red cells labeled with Fe^{59}, that the onset of shock is accompanied by the stagnation of about one-fifth of the capillary blood volume, and concluded that the downhill course in shock results from this initial removal of blood from effective circulation, rather than to a progressive increase in the blood content of the tissues consequent on increasing capillary dilatation.

Cope and Moore (46) have confirmed the general results of Fine and Seligman by the use of brominated Evans Blue and Trypan Blue, and of iodinated plasma proteins, all containing radioactive halogen. They studied the relative specific activities of lymph and plasma following the intravenous injection of the tracer. In the normal dog, the tracer content of lymph from the extremities was much lower than that of plasma. After one leg was subjected to burn with hot water, the radioactivity of lymph from that leg rose abruptly to the level of plasma; in the resulting shock, the lymph from the uninjured extremities showed no such increase in its tracer content.

All these findings agree that there is no generalized increase in membrane permeability in shock, but that the capillaries of the traumatized area do become permeable to plasma proteins and the tissue cell membranes acquire an abnormal permeability to both cations and anions. These findings should be considered definitive in this important problem.

Another application of radioactive tracers to the study of shock is in connection with the theory that has been proposed, that the "biochemical failure" which determines the fatal outcome is a depletion of the "energy-rich" phosphate bonds, represented by ATP and PC, and the failure of the phosphorylation mechanism in which ATP occupies the central position. Studies with P^{32} phosphate by Goranson (101) have shown that in rats subjected to tourniquet shock there is no decrease in the PC or ATP content of the uninjured muscles, nor in the rate of turnover across the cell membrane. There is, however, a failure of the increase in membrane exchange produced by insulin. These observations make it necessary to exercise caution in accepting the postulate that the failure of phosphorylation mechanisms is the determining factor in the fatal outcome in shock.

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SYNTHESIS OF STEROIDS OF THE PROGESTERONE SERIES[1]

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The purpose of this review is the discussion of steroidal compounds which are structurally related to progesterone (X), particularly the higher and lower homologs of progesterone. In addition, certain oxygen derivatives of progesterone and compounds less saturated than progesterone will be included. The physiological activities of these compounds will be cited insofar as they have been recorded. They will be expressed in terms of the Corner and Allen (1) test, which is based upon the endometrial changes produced by 1 mg. of progesterone (the international unit).

At the outset, a few of the familiar methods for the preparation of progesterone should be mentioned. Thus, a number of the oxidation products of cholesterol may be transformed into progesterone. Cholesterol (I), properly protected by acetylation in position 3 and bromination in positions 5,6, may be oxidized by means of chromic acid to a number of products, among which dehydroisoandrosterone (II) predominates (*cf.* 41). Minor oxidation products of practical importance are pregnenolone (III), 3(β)-hydroxy-Δ^5-etiocholenic acid (IV), and 3(β)-hydroxy-Δ^5-cholenic acid (VI). These four oxidation products may be transformed into progesterone (X). Pregnenolone (III) may be converted into this hormone (X) by means of an Oppenauer dehydrogenation.

The acetate of the 3(β)-hydroxy-Δ^5-etiocholenic acid (VII) may be transformed into the acid chloride (VIII), which on treatment with dimethylcadmium forms the acetate of pregnenolone (IX). Saponification and subsequent Oppenauer dehydrogenation yield progesterone (X) (*cf.* 21).

Recently, six methods were worked out in Miescher's laboratory (26, 29) for the transformation of 3(β)-hydroxy-Δ^5-cholenic acid (VI) into progesterone (X). Each of these methods involves from eight to eleven separate chemical steps.[2]

Dehydroisoandrosterone (II) was transformed into progesterone (X) by Butenandt and Schmidt-Thomé (4). The starting material was the acetate of dehydroisoandrosterone (XI). The cyanohydrin reaction furnished compound XII, which was dehydrated to compound XIII. A Grignard reaction yielded the methyl ketone XIV, which by partial hydrogenation with Raney nickel gave pregnenolone (III). Oppenauer dehydrogenation of this furnished pro-

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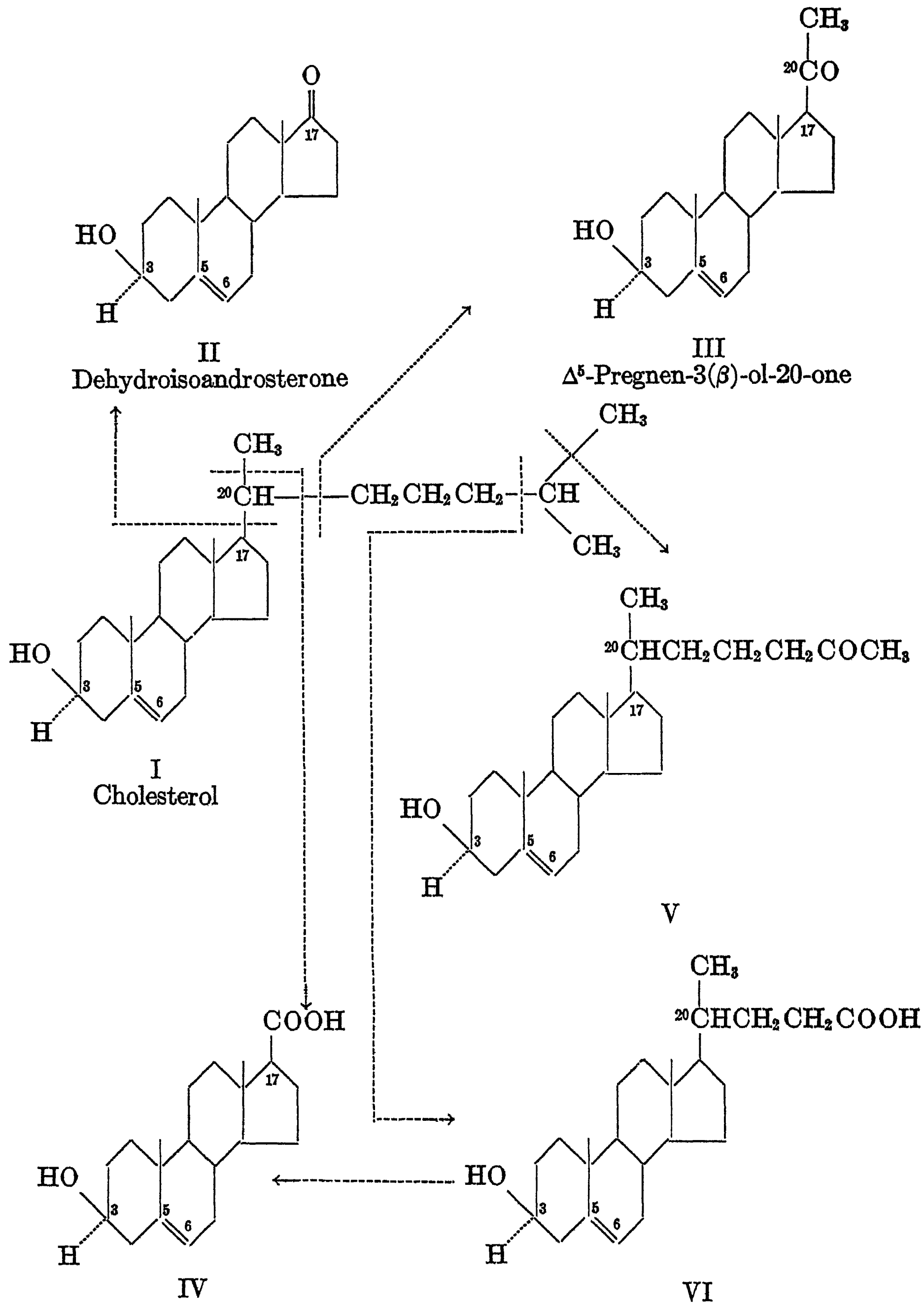
[2] While this paper was in press Billeter and Miescher (1a) established the chemical struc-



II
Dehydroisoandrosterone

III
Δ^5-Pregnen-3(β)-ol-20-one

I
Cholesterol

V

IV
3(β)-Hydroxy-Δ^5-etiocholenic acid

VI
3(β)-Hydroxy-Δ^5-cholenic acid

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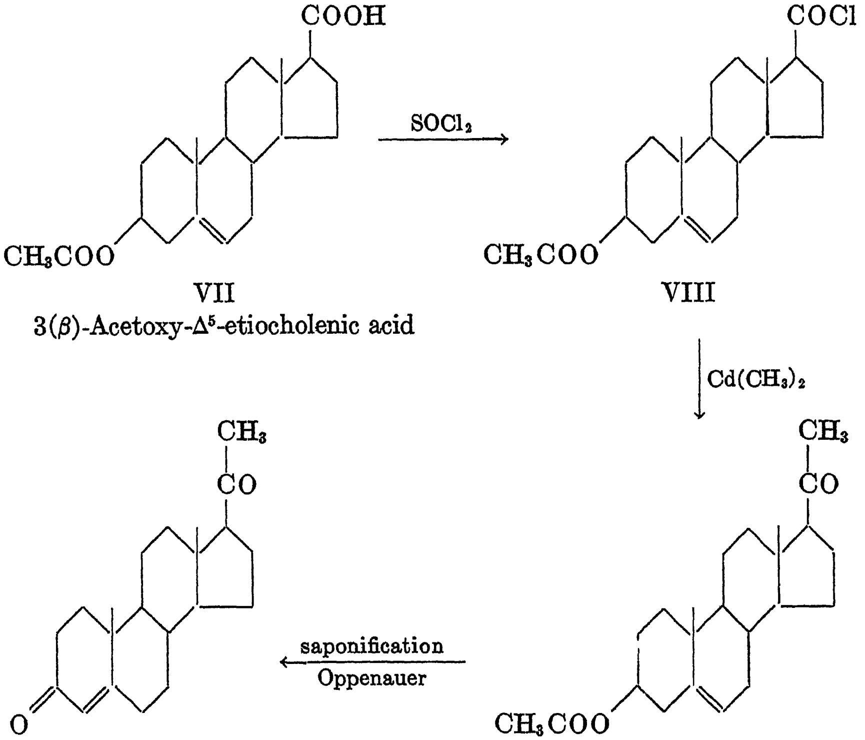
ture of another oxidation product of cholesterol as the 20-lactone of 3(β),20-dihydroxy-Δ^5-cholenic acid:



VII
3(β)-Acetoxy-Δ^5-etiocholenic acid

VIII

X
Progesterone

IX

gesterone (X). The over-all yield of this transformation is claimed to be 40 per cent. When compound XIV was directly subjected to an Oppenauer reaction, the 16-dehydroprogesterone (XV) resulted. This substance, lacking the asymmetric center at carbon atom 17, possesses no progestational activity. It may be mentioned at this point that 17-isoprogesterone, which has a configuration

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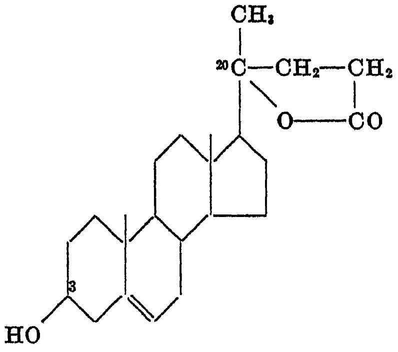
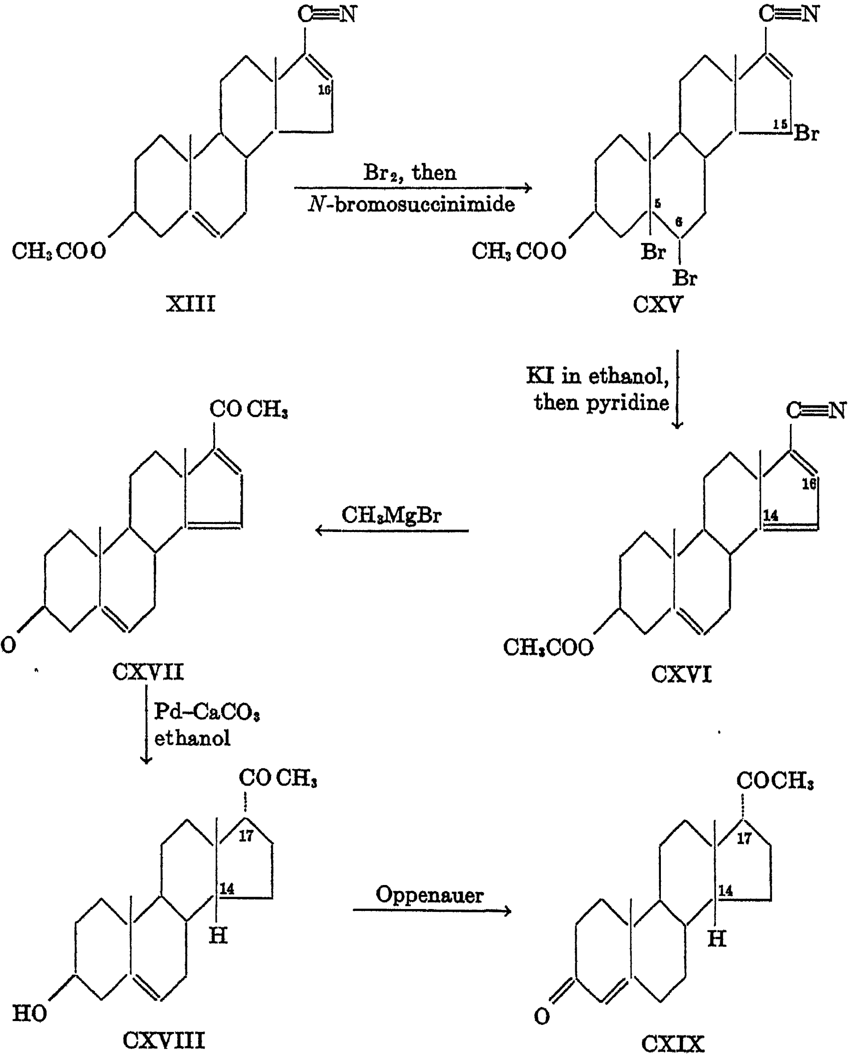
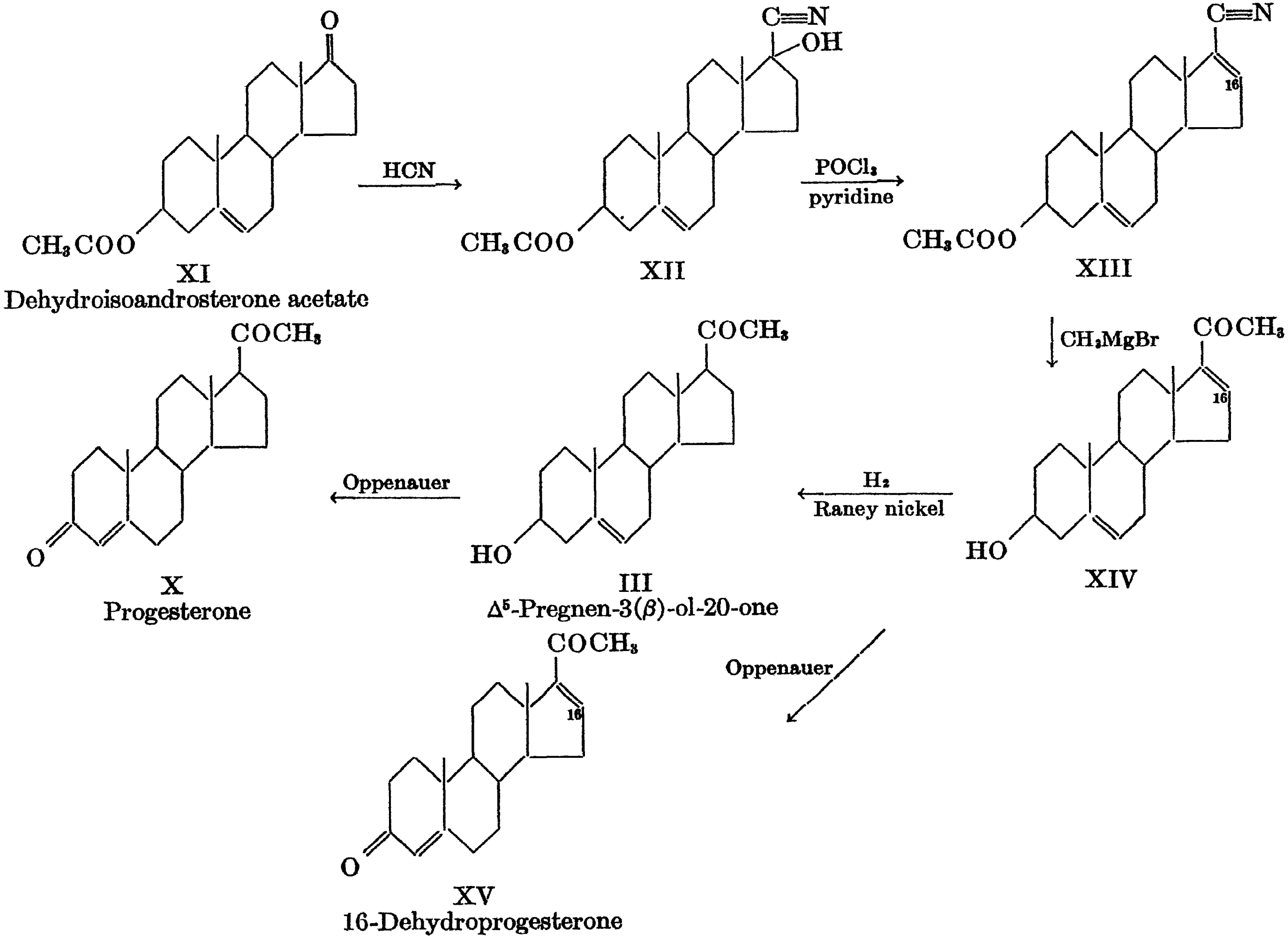


It can likewise be transformed into progesterone.

opposite to that of progesterone at carbon atom 17, is also physiologically inactive (*cf.* 5).[2a]

[2a] *Addition to proof, March 22, 1948:* In the meantime 14-allo-17-isoprogesterone (CXIX) has also been synthesized (32a). The starting material was the nitrile of 3(β)-acetoxy-$\Delta^{5,16}$-etiocholadienic acid (XIII). The 5,6-double bond was protected by adding bromine to it and a third bromine atom was introduced at carbon atom 15 by means of *N*-bromosuccinimide in the presence of light (CXV). The 5,6-double bond was reintroduced by boiling with potassium iodide in a solution of ethanol, and the resulting 15-monobromo compound was dehydrobrominated by refluxing it with pyridine. By this sequence of reactions a good yield of the nitrile of 3(β)-acetoxy-$\Delta^{5,14,16}$-etiocholatrienic acid (CXVI) was obtained. By treating this nitrile with methylmagnesium bromide the corresponding triene ketone (CXVII) was obtained, which was partially hydrogenated (palladium–calcium carbonate catalyst in ethanol) to 14-allo-17-iso-Δ^5-pregnen-3(β)-ol-20-one (CXVIII). Dehydrogenation of the latter compound by means of the Oppenauer method furnished the 14-allo-17-isoprogesterone (CXIX). It showed no progestational activity at a dosage level of 10 mg.





XI
Dehydroisoandrosterone acetate

XII

XIII

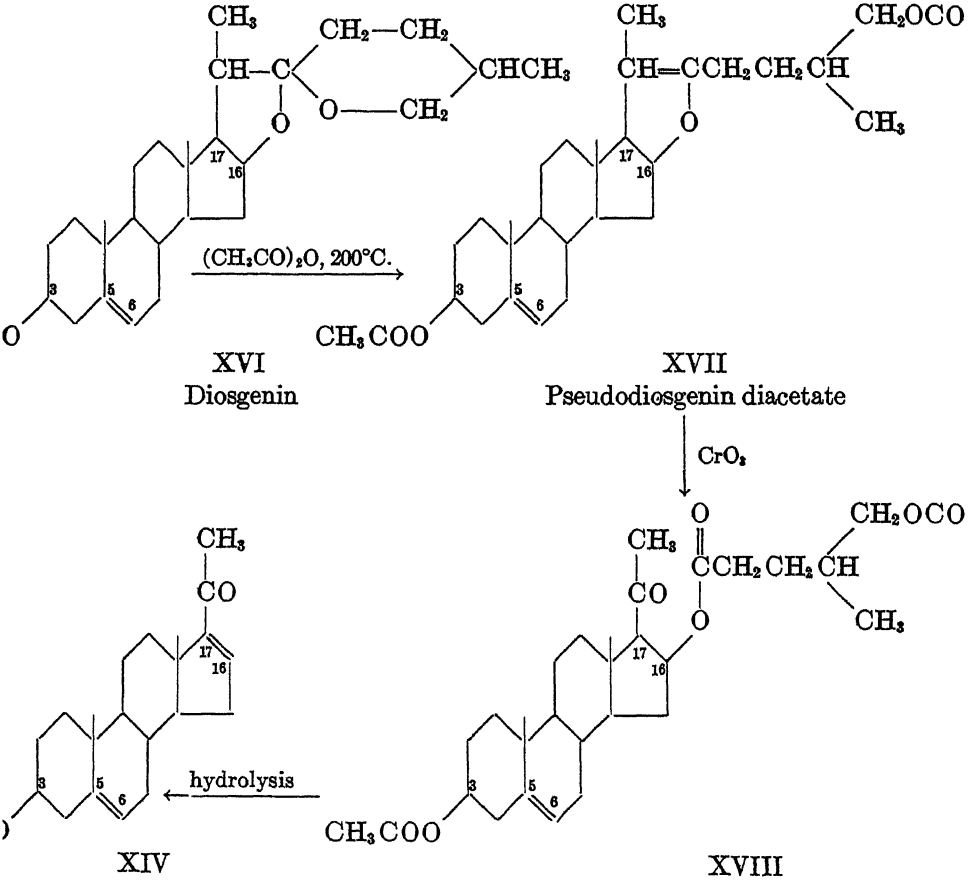
XIV

III
Δ⁵-Pregnen-3(β)-ol-20-one

X
Progesterone

XV
16-Dehydroprogesterone

In his important work on sapogenins Marker and his associates (*cf.*, e.g., 24, 24a) transformed diosgenin (XVI), which is available from a number of plants, into progesterone (X).[2b] Diosgenin (XVI), on being heated with acetic anhydride at 200°C., was converted into pseudodiosgenin diacetate (XVII). This product was oxidized with chromic acid, the protection of the double bond being unnecessary. On hydrolysis with acid or alkali, the oxidation product XVIII furnished an almost quantitative yield of $\Delta^{5,16}$-pregnadien-3(β)-ol-20-one (XIV). This substance (XIV) had already been transformed into progesterone (XIV → III → X) by Butenandt and Schmidt-Thomé (4); hence the synthesis was complete.



XVI
Diosgenin

XVII
Pseudodiosgenin diacetate

XIV
^{16}-Pregnadien-3(β)-ol-20-one

XVIII

In turning to the higher homologs of progesterone, those which are alkylated in position 16 will be discussed first. A number of such compounds were prepared by Marker and Crooks (23). The starting material was the acetate of

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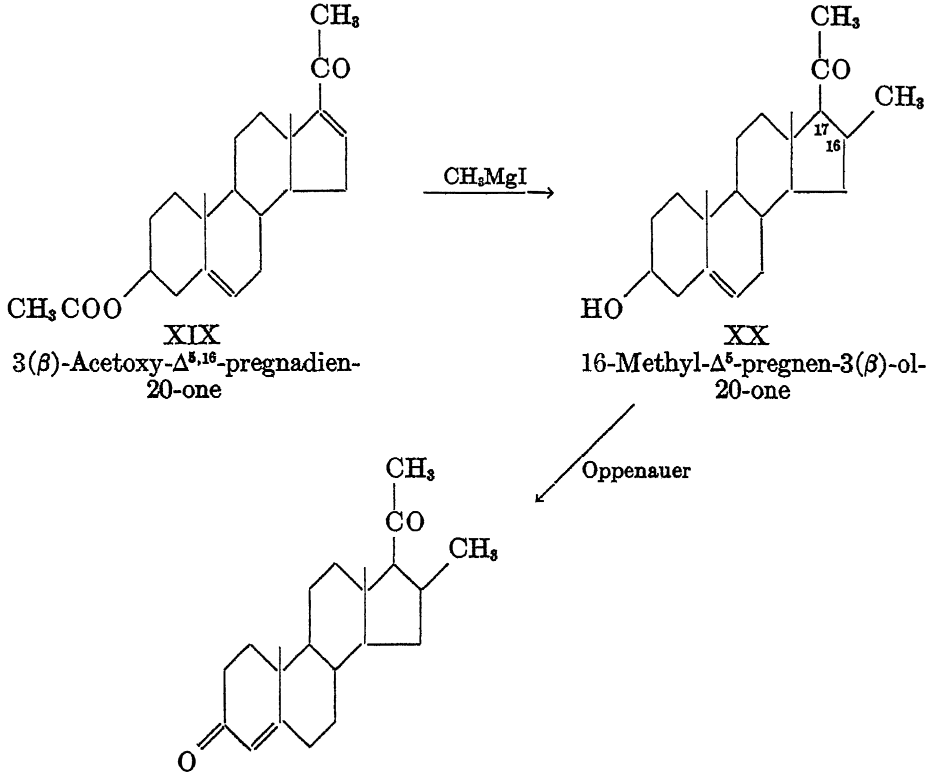
[2b] *Addition to proof, March 22, 1948:* Recently nologenin diacetate has also been transformed into progesterone (22a). The oxidation product of nologenin diacetate is identical with that of pseudodiosgenin acetate (XVIII), with the exception that it contains a hydroxyl group at carbon atom 17 instead of a hydrogen atom.

$\Delta^{5,16}$-pregnadien-3(β)-ol-20-one (XIX), which may be prepared from dehydroisoandrosterone acetate (XI) (4) or from diosgenin (XVI) (24). According to certain observations by Whitmore with Grignard compounds, it was to be expected that Grignard reagents would add to the double bond in the α,β-position to the keto group. This proved to be the case. With methylmagnesium iodide a 16-methyl-Δ^5-pregnen-3(β)-ol-20-one (XX) was obtained. A subsequent Oppenauer dehydrogenation furnished a 16-methylprogesterone (XXI) whose configurations at carbon atoms 16 and 17 remain uncertain. In an analogous fashion the 16-isopropyl- and 16-*tert*-butyl-progesterones were obtained. The physiological activities of these compounds are unknown.



XIX
3(β)-Acetoxy-$\Delta^{5,16}$-pregnadien-20-one

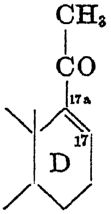
XX
16-Methyl-Δ^5-pregnen-3(β)-ol-20-one

XXI
16-Methylprogesterone

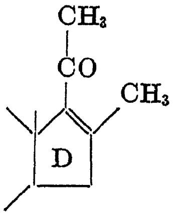
Another, chemically different, 16-methylprogesterone was described by Wettstein (50). His procedure is based upon the observation that numerous α,β-unsaturated ketones react with diazomethane with the formation of a pyrazoline-ring system. The diazomethane simply adds to the double bond in the α,β-position to the keto group. Wettstein made the interesting observation that the α,β-unsaturated ketone arrangement in ring A of the steroids presents an exception, in that it does not participate in this reaction. For instance, when he took 16-dehydroprogesterone (XV), diazomethane readily added to the double bond in ring D, yielding the crystalline pyrazoline derivative XXIX. When this compound was subjected to thermal decomposition in a vacuum, a lively evolution of nitrogen took place near the melting point. The resulting product (XXX) was purified by subsequent distillation in a high vacuum. The reaction product (XXX) differs from the starting material (XV) in that it is methylated in position 16.

In preparing his 16-methylprogesterone, Wettstein performed a similar sequence of reactions starting with $\Delta^{5,16}$-pregnadien-3(β)-ol-20-one (XIV) or its acetate (XIX). Taking the free alcohol (XIV), treatment with diazomethane furnished the pyrazoline XXII, which was decomposed to the 16-methyl derivative (XXIII). Subsequent acetylation furnished the acetate XXIV. The identical acetate was obtained also by starting with the acetate XIX, treating it with diazomethane, and subsequently decompositing the pyrazoline XXVIII. The diene acetate XXIV was partially hydrogenated with nickel as catalyst, yielding compound XXV. Though this hydrogenation may theoretically lead to four different isomers, actually only one compound was isolated. Various considerations, especially comparisons of optical rotations, make it probable that the isolated substance possesses a normal configuration at carbon atom 17. The configuration at carbon atom 16 remains unknown. Saponification of compound XXV yielded the 16-methyl-Δ^5-pregnen-3(β)-ol-20-one (XXVI), which by means of an Oppenauer dehydrogenation was transformed into a 16-methylprogesterone (XXVII). Physiological data on this 16-methylprogesterone are not available.

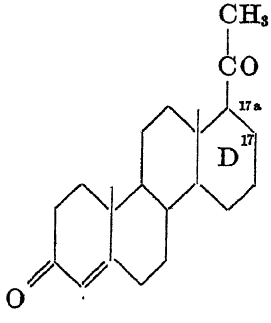
It is not impossible that the decomposition of the pyrazolines is associated with a ring enlargement. This would yield, instead of the methylated five-membered ring, a six-membered ring D:



instead of

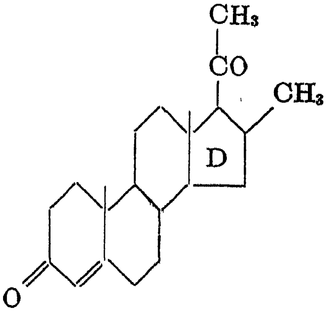


The end product might therefore be a D-homoprogesterone instead of a 16-methylprogesterone:

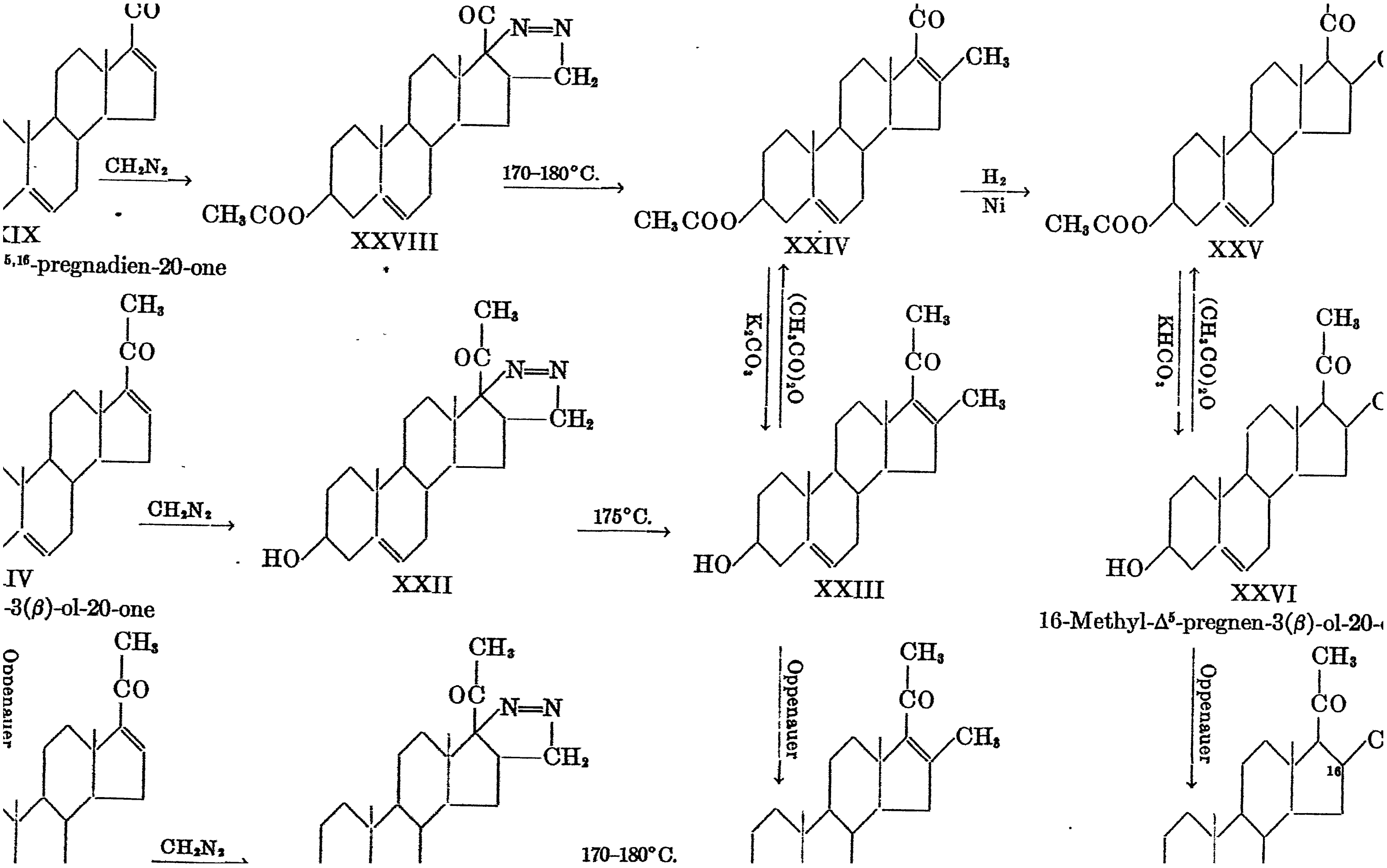


D-Homoprogesterone

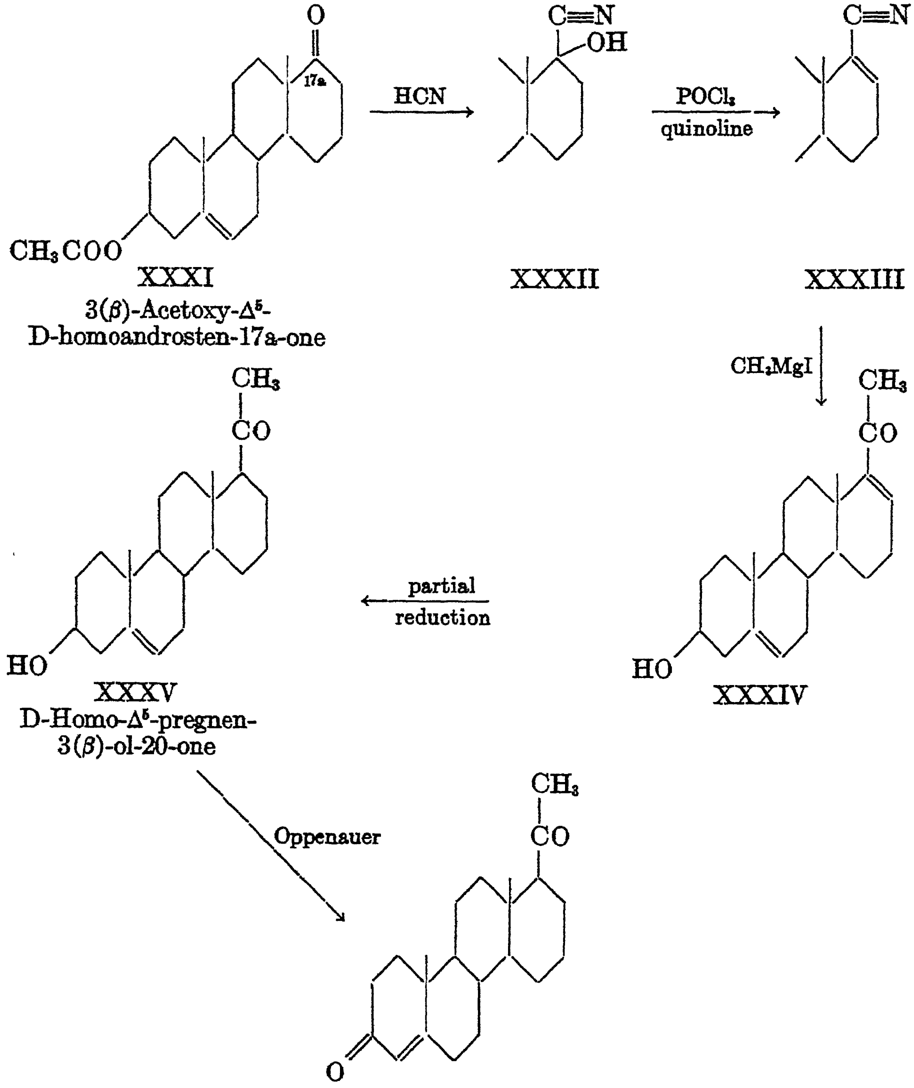
instead of



XXVII
16-Methylprogesterone


CO
CH₂N₂
XIX
⁵,¹⁶-pregnadien-20-one
OC
N=N
CH₂
CH₃COO
XXVIII
170–180°C.
CO
CH₃
CH₃COO
XXIV
H₂
Ni
CO
CH₃COO
XXV
(CH₃CO)₂O
K₂CO₃
(CH₃CO)₂O
KHCO₃
CH₃
CO
IV
-3(β)-ol-20-one
CH₂N₂
CH₃
OC
N=N
CH₂
HO
XXII
175°C.
CH₃
CO
CH₃
HO
XXIII
CH₃
CO
HO
XXVI
16-Methyl-Δ⁵-pregnen-3(β)-ol-20-
Oppenauer
CH₃
CO
CH₂N₂
CH₃
OC
N=N
CH₂
170–180°C.
Oppenauer
CH₃
CO
CH₃
Oppenauer
CH₃
CO
16
C

It may be mentioned that a D-homoprogesterone (XXXVI) and also a D-homodesoxycorticosterone are claimed by Ruzicka and Goldberg (39) in Swiss and American patents. In the American patent the preparation of the D-homoprogesterone is described only in the most general terms. No chemical characteristics of the intermediates or end product are given. In the disclosure it is stated that compounds of this type possess high physiological activity. According to the patent the preparation of D-homoprogesterone proceeds as follows:



XXXI
3(β)-Acetoxy-Δ^5-D-homoandrosten-17a-one

XXXII

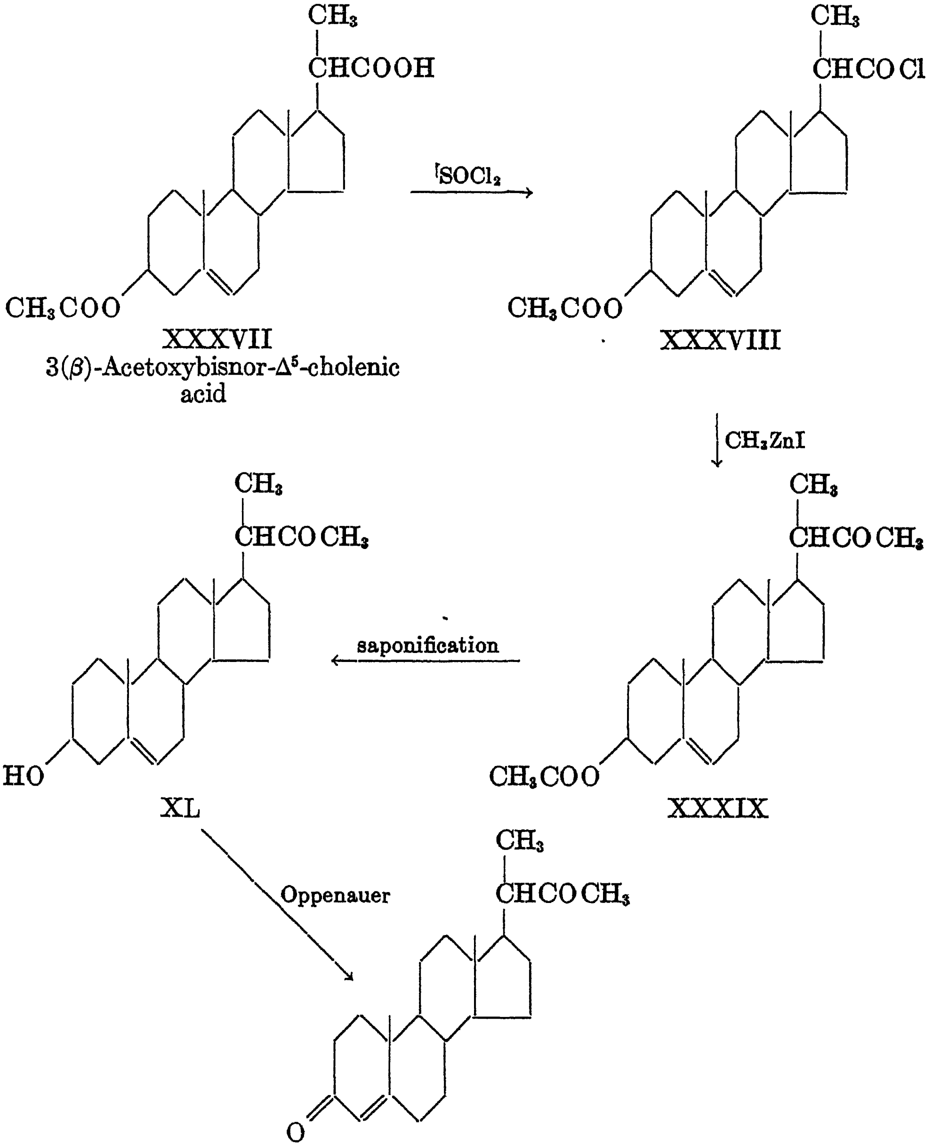
XXXIII

XXXIV

XXXV
D-Homo-Δ^5-pregnen-3(β)-ol-20-one

XXXVI
D-Homoprogesterone

The method appears completely analogous to Butenandt's procedure (4) of preparing progesterone from dehydroisoandrosterone. However, since the patent does not contain any details regarding the procedures nor any characteristics of the substances claimed, it appears somewhat doubtful whether these compounds have been sufficiently characterized. No publication covering the same substances has ever appeared in a chemical journal. It would certainly be interesting to prepare such compounds and test them for their physiological action. As is known, D-homoandrostane derivatives (*cf.*, e.g., 15a, 17) generally



XXXVII
3(β)-Acetoxybisnor-Δ^5-cholenic acid

XXXVIII

XXXIX

XL

XLI
Nor-Δ^4-cholene-3,22-dione

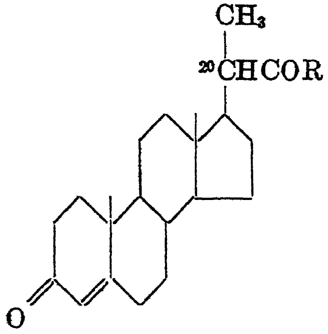
possess the same order of androgenic activity as the corresponding androstane derivatives. On the other hand, the D-homo analogs of estrone and estradiol (*cf.*, e.g., 16) seem to possess no estrogenic activity.

More is known regarding the physiological activity of the side-chain homologs of progesterone. The higher homologs derived from progesterone in this fashion fall in two groups.

In the first group carbon atoms appear introduced between carbon atom 17 and the keto group of the side chain. This will be illustrated by two examples.

(*a*) The higher homolog, nor-Δ^4-cholene-3,22-dione (XLI), was prepared by Wettstein (49) from 3(β)-acetoxybisnor-Δ^5-cholenic acid (XXXVII). This acid had been obtained previously by Fernholz in his studies on the degradation of stigmasterol. The acid chloride XXXVIII yielded with methylzinc iodide the ketone XXXIX, which was saponified to the free alcohol XL. The latter was dehydrogenated according to the Oppenauer method, yielding compound XLI.

Cole and Julian (6) have carried out analogous experiments on an extensive scale. Starting material for their work was the acid chloride XXXVIII, which was successfully treated with a number of dialkylcadmium compounds. They were even able to isolate end products (XLII) epimeric at carbon atom 20.



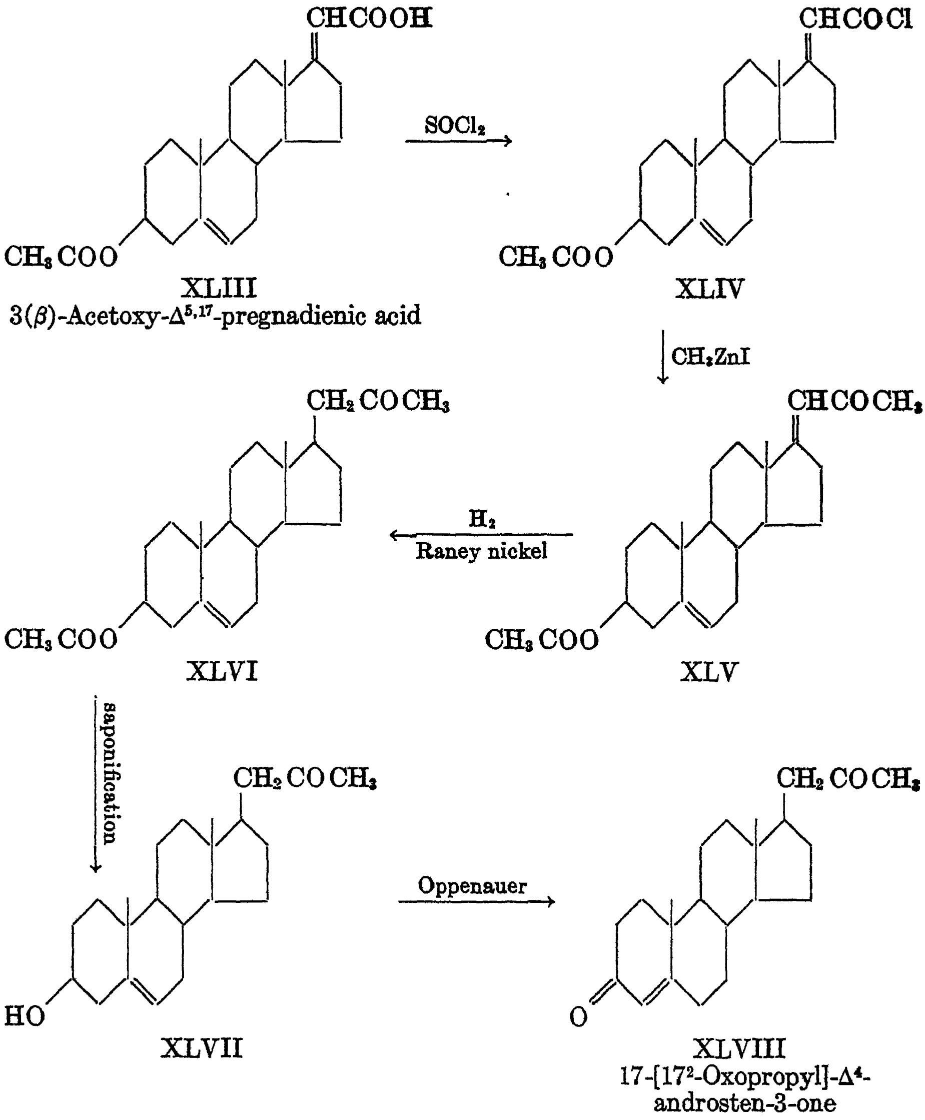
XLII

R = methyl, ethyl, isoamyl

All homologs of this series lacked progestational activity.

(*b*) The higher homolog 17-[17^2-oxopropyl]-Δ^4-androsten-3-one (XLVIII) was prepared by Plattner and Schreck (36) from 3(β)-acetoxy-$\Delta^{5,17}$-pregnadienic acid (XLIII). This acid is accessible from dehydroisoandrosterone (II) by means of a Reformatzky reaction and subsequent dehydration (35). The acid chloride (XLIV) was treated with methylzinc iodide, yielding the ketone XLV, which by means of partial hydrogenation with Raney nickel furnished compound XLVI. The stereochemical configuration at carbon atom 17 remains uncertain. Saponification of compound XLVI furnished compound XLVII which, by means of an Oppenauer dehydrogenation, was transformed into the progesterone homolog XLVIII.

A second group of higher side-chain homologs is derived from progesterone, in that a radical replaces a hydrogen atom at carbon atom 21. Compounds of this



type can easily be prepared from the acid chloride of 3(β)-acetoxy-Δ^5-etiocholenic acid (XLIX). Wettstein (48) reacted this compound with diethylzinc and propylzinc iodide, respectively, obtaining compounds La and Lb. A variant in the preparation of these substances consisted in treating the acid chloride (XLIX) with suitable malonic ester derivatives. Saponification of compounds La and Lb, followed by Oppenauer dehydrogenation, furnished 21-methylprogesterone (LIa) and 21-ethylprogesterone (LIb), respectively. 21-Methylprogesterone (LIa) was active with 3 mg. in the Clauberg test, i.e., equivalent to about 6 mg. in the Corner-Allen test, but 21-ethylprogesterone (LIb) proved to be physiologically inactive. Considering that progesterone is active at a dosage level of 1 mg., this indicates that lengthening of the side chain by substitution at carbon atom 21 decreases the physiological activity. It may be added that Marker and his associates (25) have prepared 21-benzalprogesterone (LIII) and 21-benzylprogesterone (LVII). Pregnenolone acetate (IX) was condensed with benzaldehyde to the benzal derivative LII, which by means of the Oppenauer dehydrogenation was transformed into 21-benzalprogesterone (LIII). When the benzalpregnenolone (LII) was acetylated (LIV), partially hydrogenated (LV), saponified (LVI), and finally treated according to Oppenauer, the end product was 21-benzylprogesterone (LVII). No physiological activity has been recorded for 21-benzalprogesterone (LIII) and 21-benzylprogesterone (LVII).

A lower member in the series of the side-chain homologs is 20-norprogesterone (LXII), which was prepared by Miescher, Hunziker, and Wettstein (30). In this homolog the methyl group of the side chain of progesterone is replaced by a hydrogen atom. The starting meterial for this synthesis was 21-acetoxy-Δ^5-pregnen-3(β)-ol-20-one (LVIII), which is known to be an intermediate in Reichstein's synthesis of desoxycorticosterone. Steiger and Reichstein (45) had already transformed this easily available substance into compound LXI in the following fashion: By means of the Meerwein–Ponndorff method the keto group was reduced to a secondary alcohol group; subsequent saponification yielded the triol LIX. Although two epimeric forms are possible at carbon atom 20, one of them predominated in the reaction mixture. It was transformed into the acetone compound LX which, by means of an Oppenauer dehydrogenation, furnished an α,β-unsaturated ketone. Subsequent hydrolysis of the acetonide yielded compound LXI. Oxidation under suitable conditions with periodic acid furnished the 20-norprogesterone (LXII). This substance was active at a dosage level of 10–20 mg. in the Clauberg test, which is the equivalent of about 20–40 mg. in the Corner–Allen test. Hence this lower homolog of progesterone possesses only very slight progestational activity.

Another lower homolog is 10-norprogesterone. It is derived from progesterone in that the angular methyl group at carbon atom 10 is replaced by a hydrogen atom. This compound was prepared by Ehrenstein (8) and found to be very active (1). The starting material was strophanthidin (LXIII), which possesses the general structural features of the cardiac aglycones. The structure is identical with that of periplogenin (LXIV), except that an aldehyde group instead of a methyl group is attached to carbon atom 10 (8). The configurational formulas of strophanthidin and periplogenin have been revised on the basis of recent investigations by Speiser and Reichstein (44).[3] All functional groups, i.e., the hydroxyl groups in positions 3,5,14 and the lactone ring in position 17, are probably attached in the β-position. Some of the intermediates described by Ehrenstein (8) had been reported in the literature previously (8).

Jacobs (20) oxidized strophanthidin (LXIII) with potassium permanganate in a neutral solution of acetone and obtained the monobasic strophanthidinic acid (LXVI). Under these conditions the unsaturated lactone ring remained intact.

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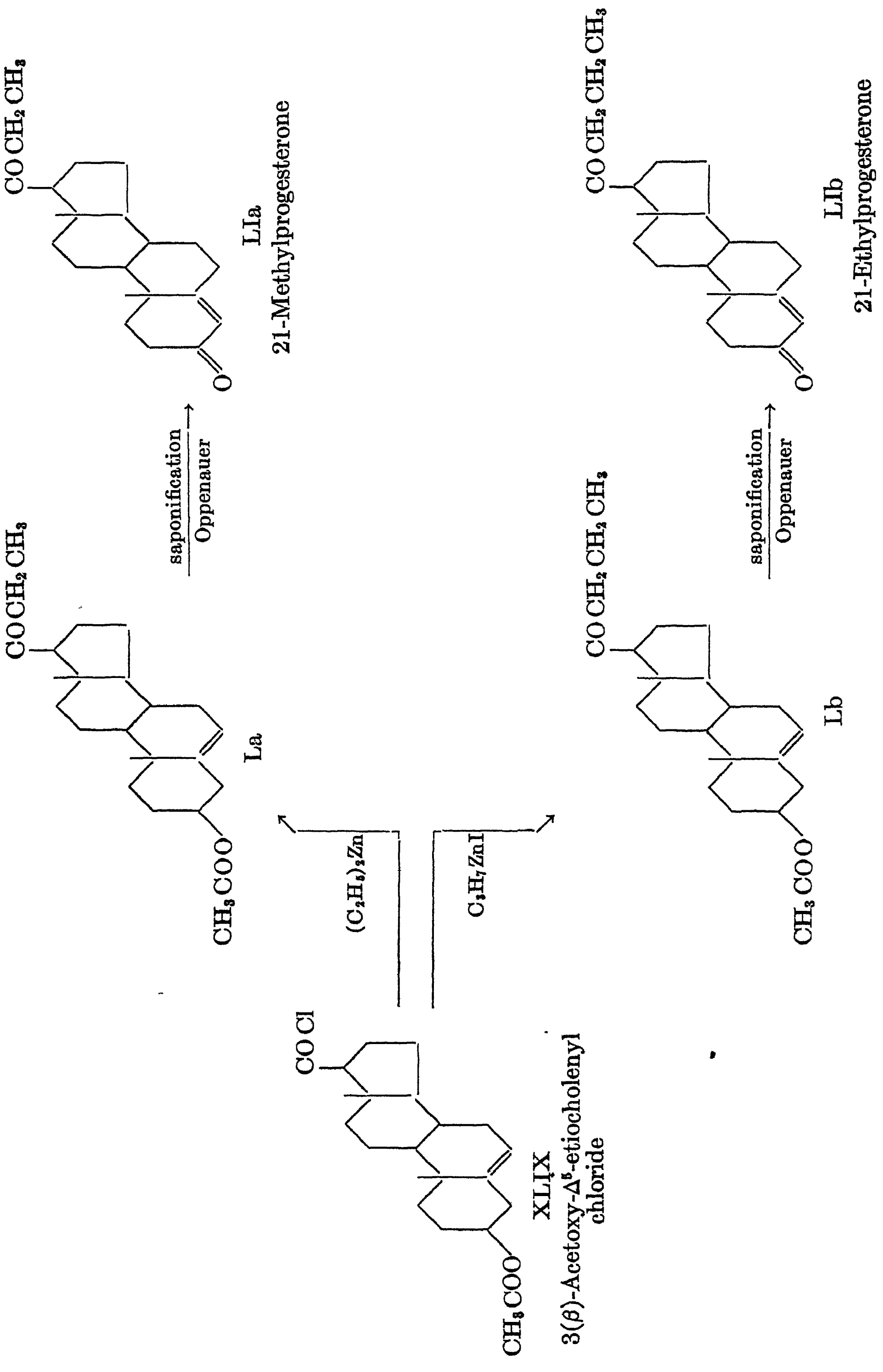
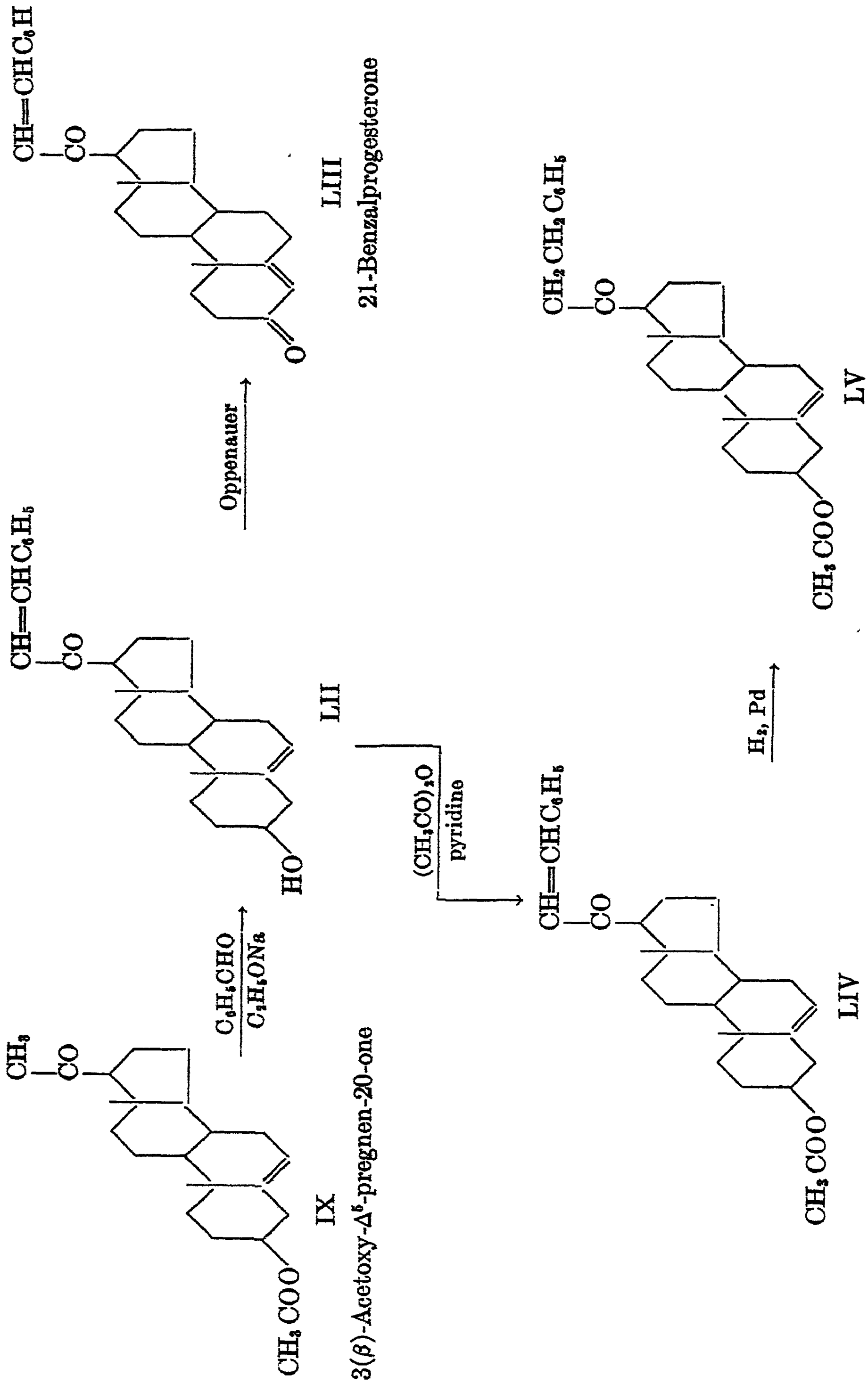
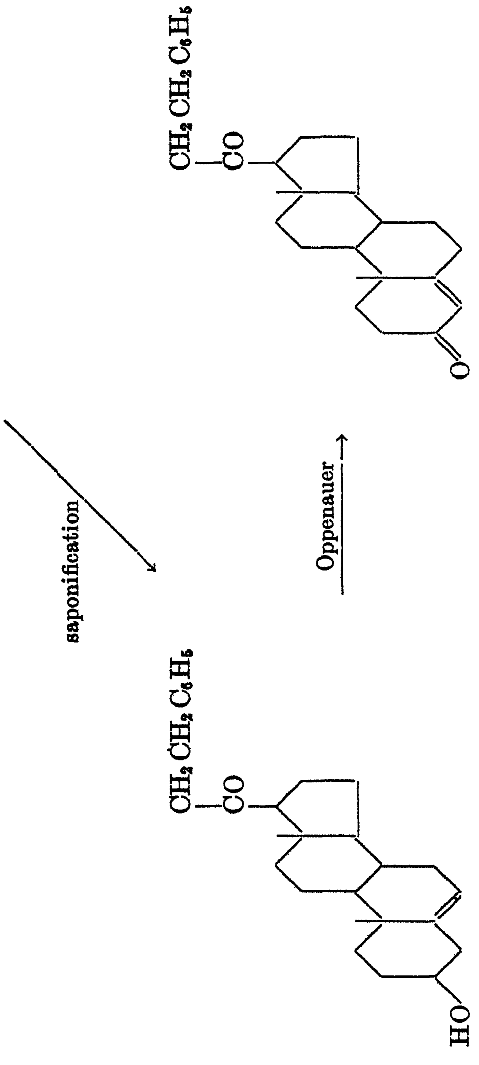
[3] *Cf.* the more recent article, "On the stereochemistry of strophanthidin and periplogenin" (36a).

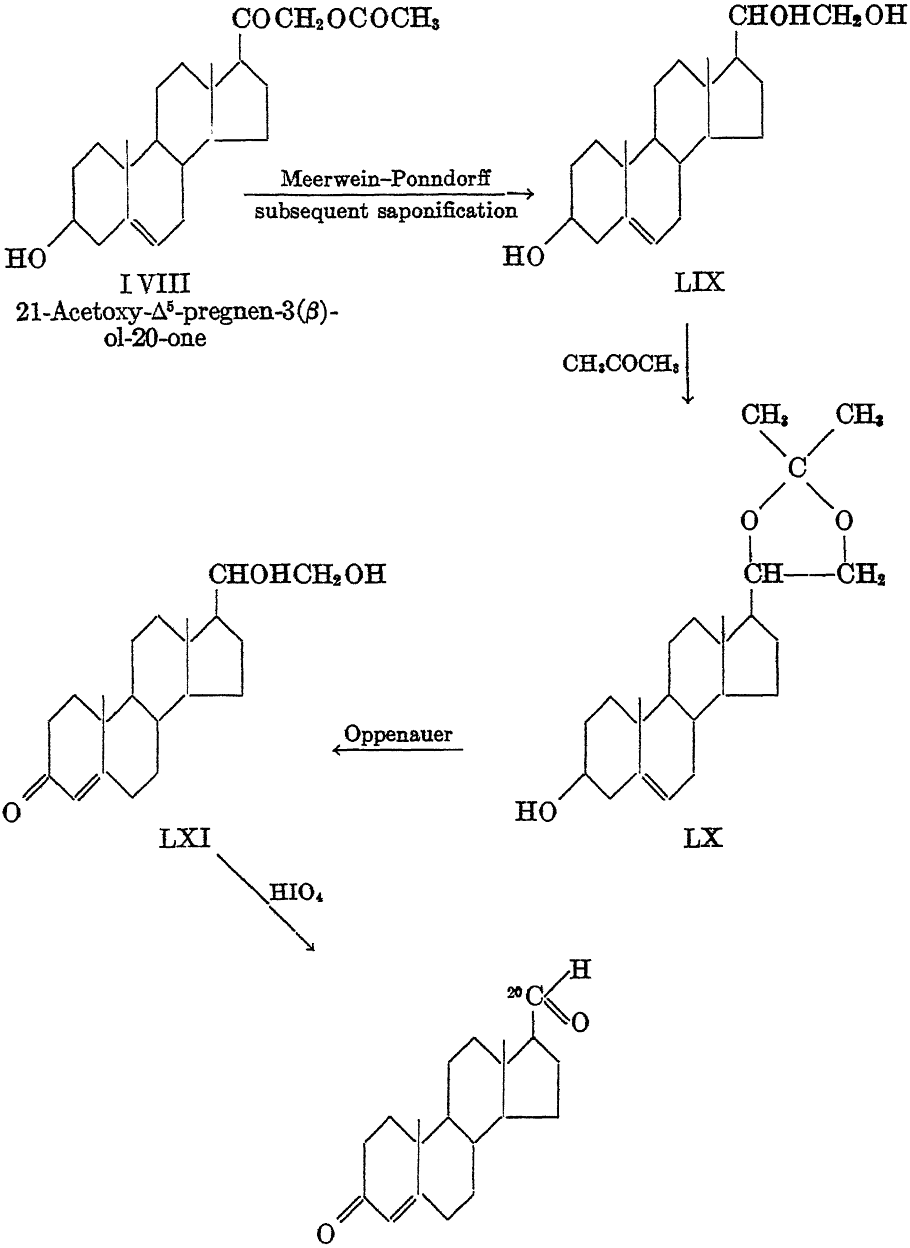

COCl
CH₃COO
XLIX
3(β)-Acetoxy-Δ⁵-etiocholenyl chloride
(C₂H₅)₂Zn
C₃H₇ZnI
COCH₂CH₃
CH₃COO
La
COCH₂CH₂CH₃
CH₃COO
Lb
saponification
Oppenauer
COCH₂CH₃
O
LIa
21-Methylprogesterone
COCH₂CH₂CH₃
O
LIb
21-Ethylprogesterone


CH₃
CO
CH₃COO
IX
3(β)-Acetoxy-Δ⁵-pregnen-20-one
C₆H₅CHO
C₂H₅ONa
CH=CHC₆H₅
CO
HO
LII
Oppenauer
CH=CHC₆H₅
CO
O
LIII
21-Benzalprogesterone
(CH₃CO)₂O
pyridine
CH=CHC₆H₅
CO
CH₃COO
LIV
H₂, Pd
CH₂CH₂C₆H₅
CO
CH₃COO
LV



LVI

LVII
21-Benzylprogesterone



LVIII
21-Acetoxy-Δ^5-pregnen-3(β)-ol-20-one

LIX

LX

LXI

LXII
20-Norprogesterone

When the acid (LXVI) was subjected to oxidation with potassium permanganate in an alkaline solution, compound LXVII, which is an α-ketolactone acid, was obtained. Lactonization has occurred because the side chain attached to carbon atom 17 and the hydroxyl group at carbon atom 14 are in the *cis* position. On boiling this ketolactone acid LXVII with alkali, the lactone ring opened and simultaneous epimerization took place at carbon atom 17, obviously by way of enolization of the carbonyl group adjacent to carbon atom 17. Through this epimerization the side chain at carbon atom 17 is placed in the so-called "iso position", which in this case is *trans* to the hydroxyl group at carbon atom 14, a configuration which prevents relactonization. Elderfield (14) subjected the dicarboxylic acid LXVIII to further degradation by means of hydrogen peroxide and obtained the dicarboxylic acid LXIX. Butenandt and Gallagher (3) dehydrated acid LXIX under mild conditions and obtained the unsaturated dicarboxylic acid LXX, which in turn was hydrogenated to the saturated dicarboxylic acid LXXI. The stereochemical configuration of this compound (LXXI), in particular at carbon atom 14, remains uncertain. According to recent observations by Ruzicka (*cf.*, e.g., 33, 34, 40, 44) the stereochemical course of the hydrogenation of Δ^{14}-unsaturated 17-carboxylic acids or their esters depends entirely on the configuration at carbon atom 17. A normal configuration at C_{17} leads to a *trans* linkage of rings C and D, whereas an iso configuration at C_{17} leads to a *cis* linkage. Provided the carboxyl group at carbon atom 10 does not influence this rule, the linkage between rings C and D in compound LXXI may be *cis*, as tentatively indicated in formula LXXI. However, this configuration cannot be assigned with certainty. The transformation of LXIX into LXXI was carried out simultaneously with practically identical results in the laboratories of both Butenandt (3) and Ehrenstein (8). The latter transformed the dibasic acid LXXI into the monoacetyl derivative LXXII and subjected it to a distillation in a high vacuum. Such treatment brings about simultaneous dehydration and decarboxylation. The double bond of the reaction product is probably in the 5,6-position, as indicated by formula LXXIII, although the alternatives LXXIIIa and LXXIIIb cannot be ruled out. The configuration at the asymmetric carbon atom 10 remains unknown. The acid chloride LXXIV was treated with methylzinc iodide, leading to the methyl ketone LXXV. Subsequent saponification yielded a 10-norpregnenolone (LXXVI). This reaction may have brought about an inversion of the configuration at carbon atom 17 leading from the iso to the normal arrangement,[4] though according to very recent evidence this appears improbable.[5] Dehydrogenation of the 10-norpregnenolone (LXXVI) according to the Oppenauer method yielded a 10-norprogesterone (LXXVII). By established methods the acid chloride LXXIV was also transformed into a 10-nor-11-desoxycorticosterone acetate. Although these two end products were non-crystalline, they have been fully characterized. The configurations at carbon atoms 10, 14, and 17 remain uncertain.[5a] It is perhaps a

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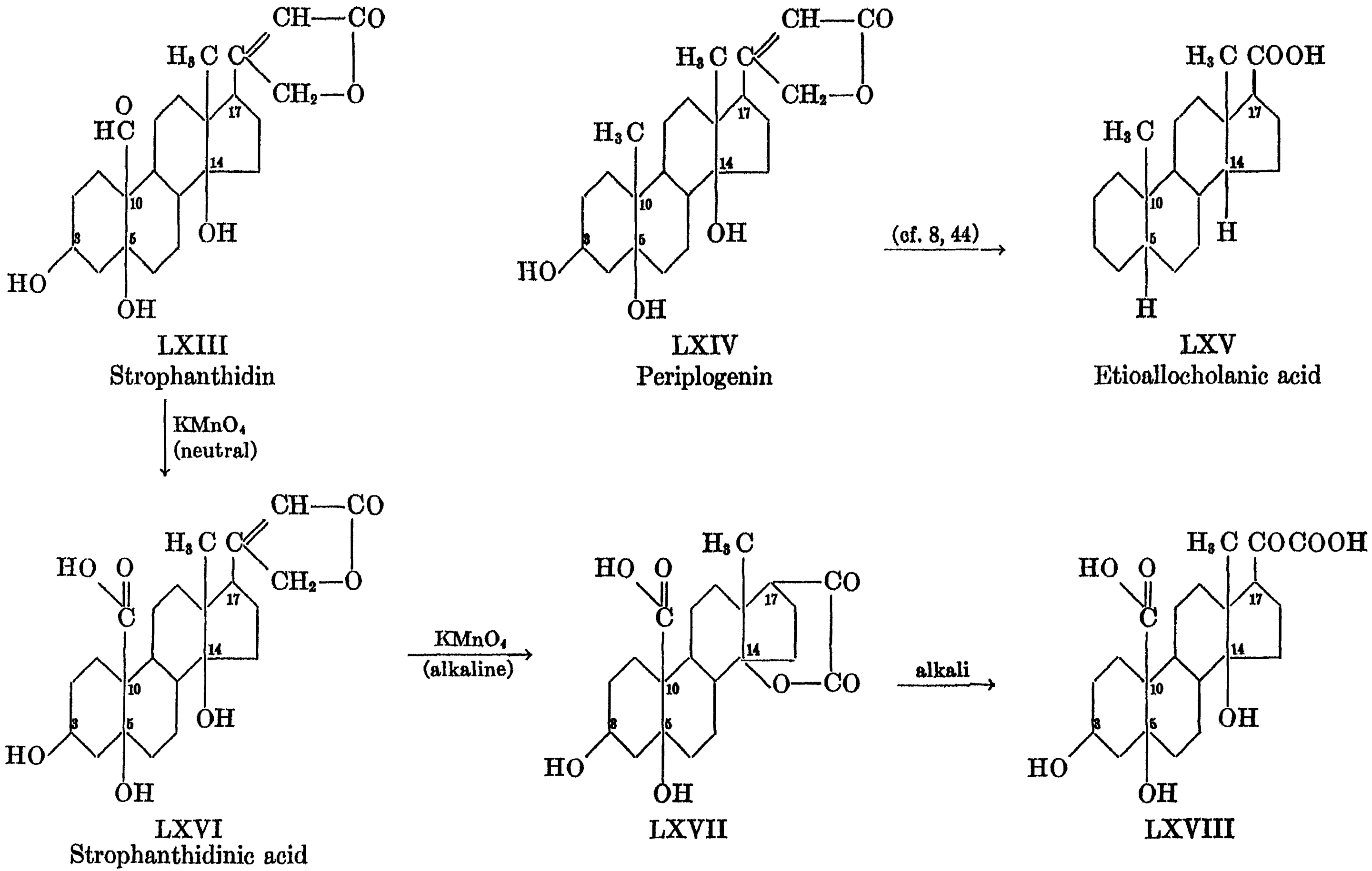
[4] For reasons *cf.* reference 8, page 441.

[5] 20-Keto-17-isosteroids with the iso configuration at carbon 14 appear to be stable towards acid and alkali (25a; *cf.* page 2025).

[5a] *Addition to proof, March 22, 1948:* In two recent publications (5a, 32a) it is suggested that the 10-norprogesterone prepared by Ehrenstein (8) possesses the iso (allo) configuration at carbon atom 14 and the iso configuration at carbon atom 17, as tentatively expressed in formula LXXVII. This cannot be considered definitely proven, and the stereochemical arrangement at carbon atom 10 remains wholly uncertain. Experiments are under way in the author's laboratory to repeat the preparation of 10-norprogesterone with such modifications that the isolation of stereochemically uniform material will be possible.



LXIII Strophanthidin

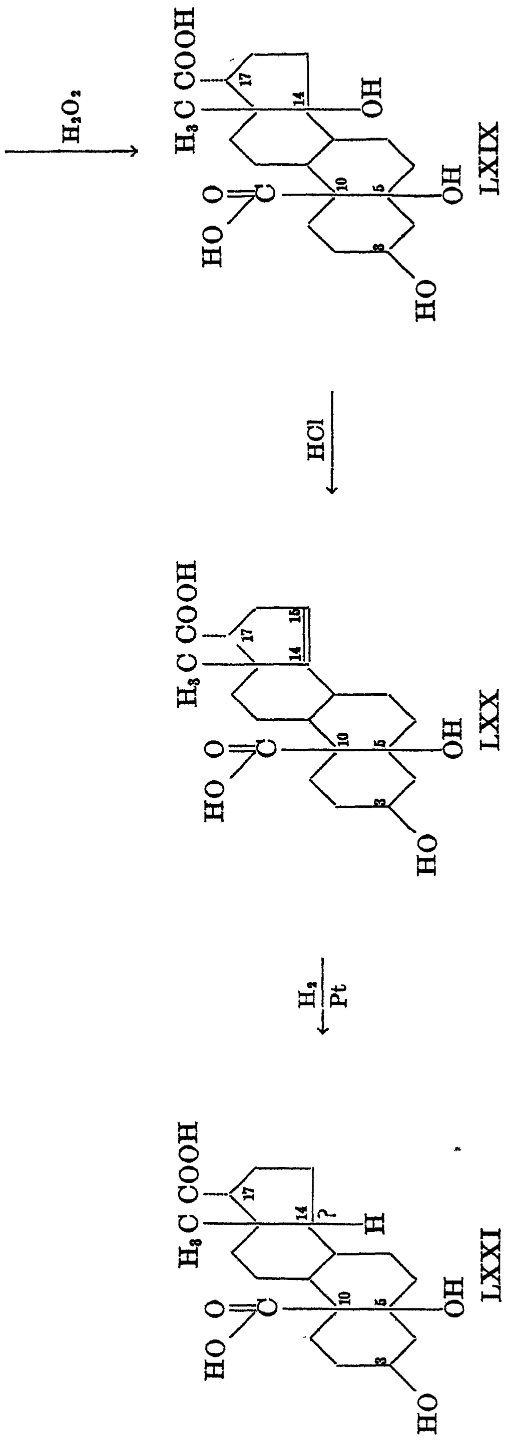
LXIV Periplogenin

LXV Etioallocholanic acid

LXVI Strophanthidinic acid

LXVII

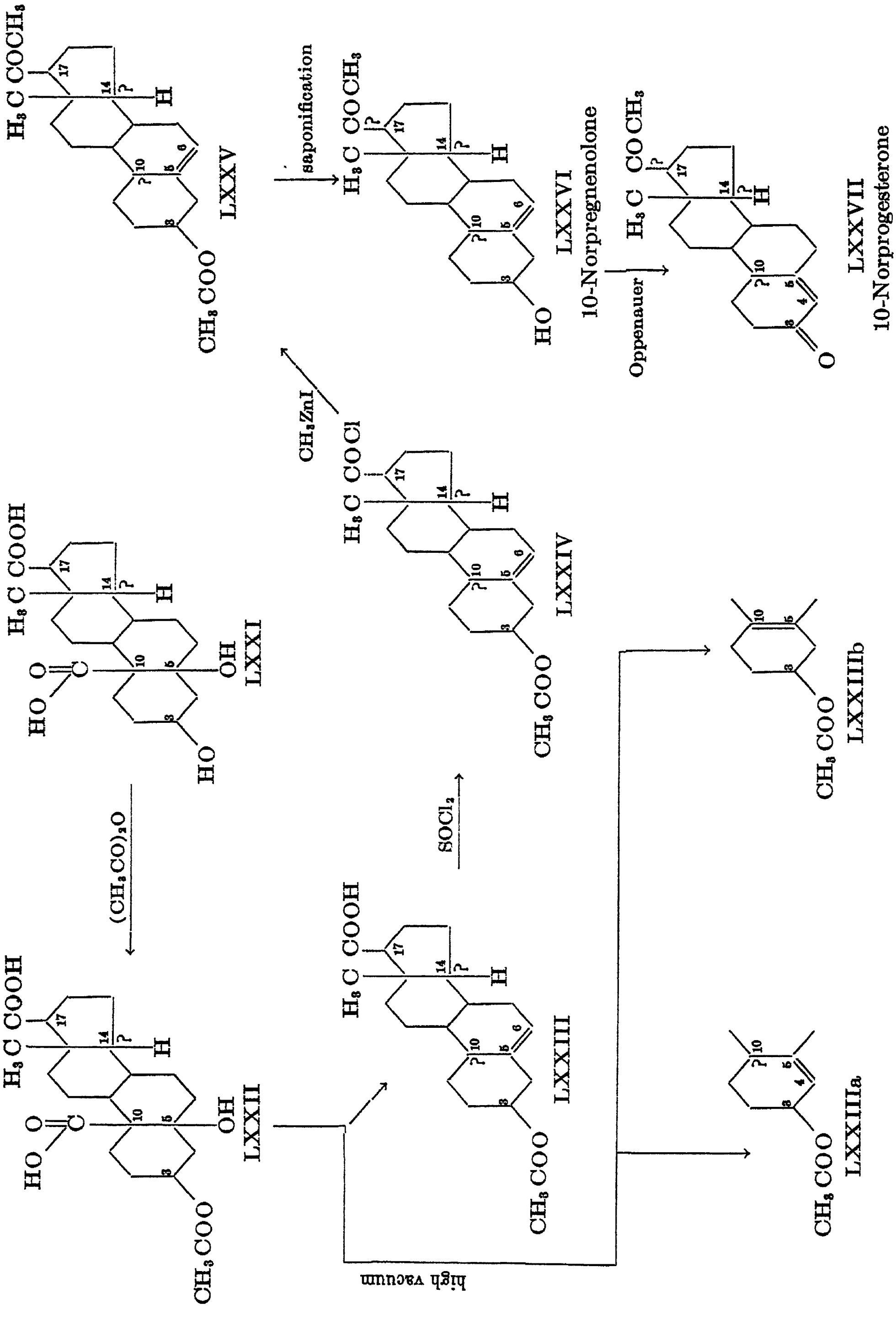
LXVIII



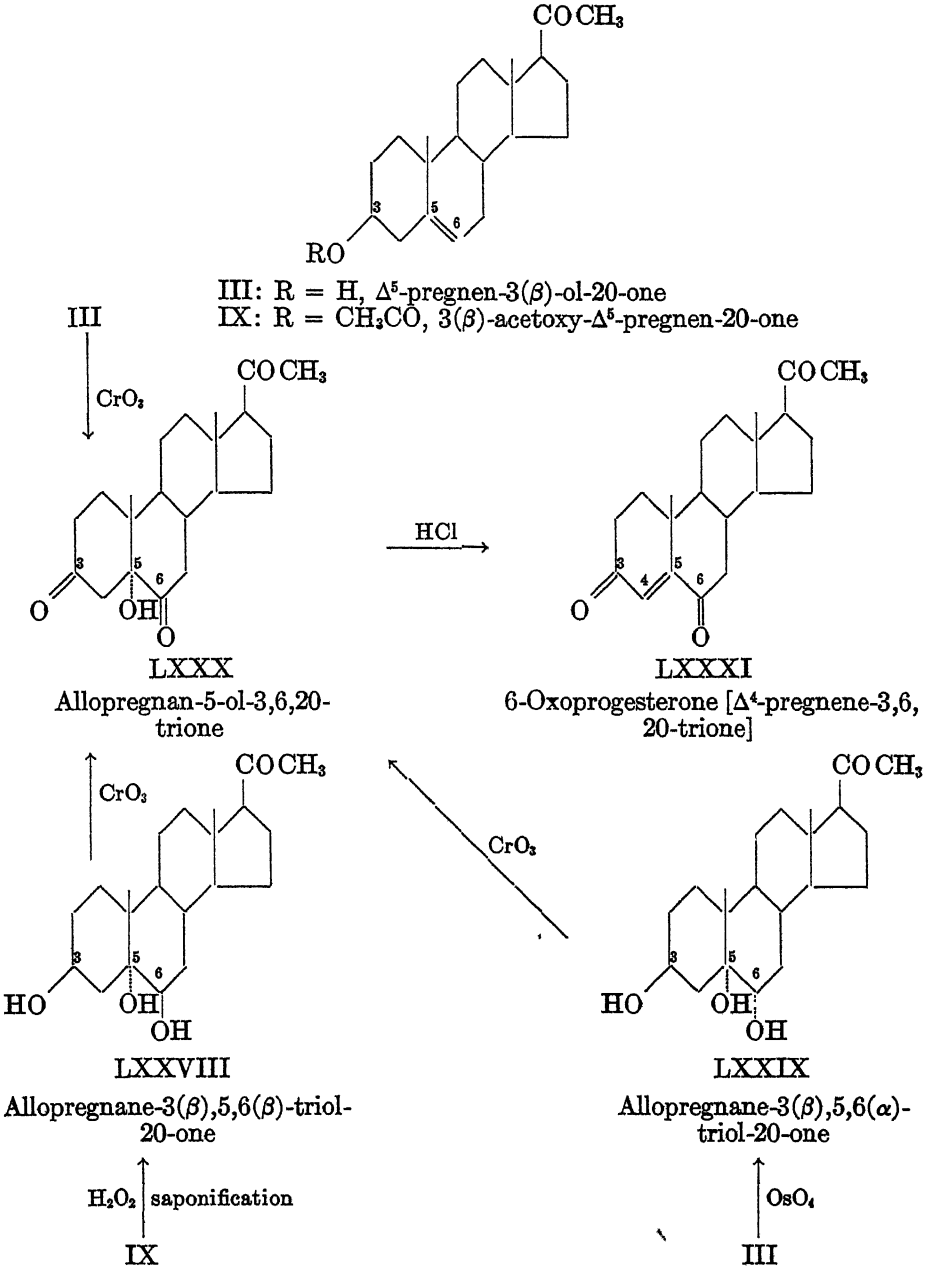
LXIX

LXX

LXXI


LXXI
$(CH_3CO)_2O$
LXXII
high vacuum
LXXIII
$SOCl_2$
LXXIV
CH_3ZnI
LXXV
saponification
LXXVI
10-Norpregnenolone
Oppenauer
LXXVII
10-Norprogesterone
LXXIIIa
LXXIIIb

stereochemical mixture. The 10-norprogesterone was tested for progestational activity (1) and found to be at least as active as progesterone. This physiological finding indicates that the angular methyl group between rings A and B is not essential for progestational activity. Considering that this preparation of 10-norprogesterone may be a stereochemical mixture, one of its components may



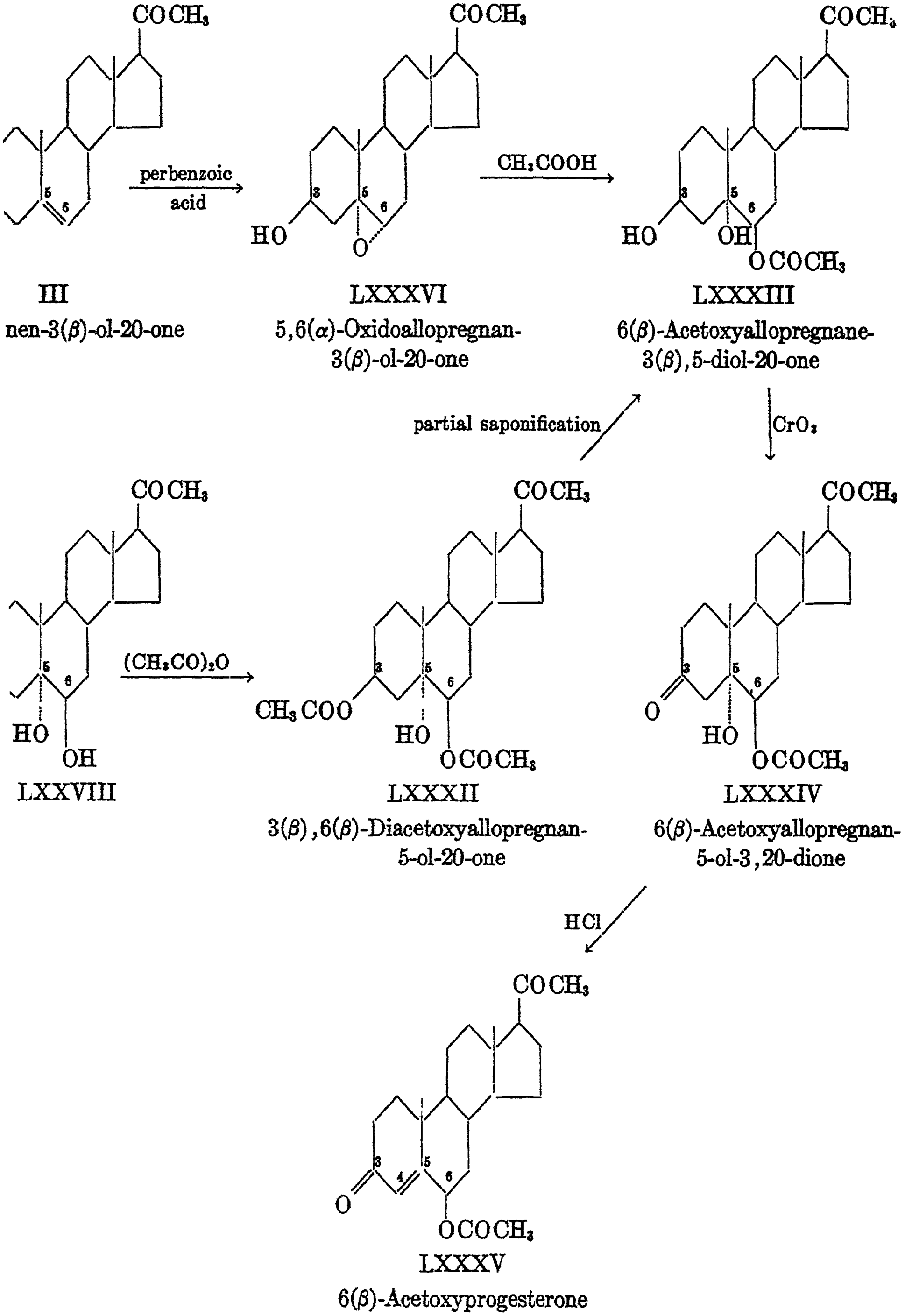
III: R = H, Δ^5-pregnen-3(β)-ol-20-one
IX: R = CH_3CO, 3(β)-acetoxy-Δ^5-pregnen-20-one

LXXX
Allopregnan-5-ol-3,6,20-trione

LXXXI
6-Oxoprogesterone [Δ^4-pregnene-3,6,20-trione]

LXXVIII
Allopregnane-3(β),5,6(β)-triol-20-one

LXXIX
Allopregnane-3(β),5,6(α)-triol-20-one


COCH₃
5
6
perbenzoic acid
III
nen-3(β)-ol-20-one
COCH₃
HO
3
5
6
O
LXXXVI
5,6(α)-Oxidoallopregnan-3(β)-ol-20-one
CH₃COOH
COCH₃
HO
3
5
6
OH
OCOCH₃
LXXXIII
6(β)-Acetoxyallopregnane-3(β),5-diol-20-one
partial saponification
CrO₃
COCH₃
5
6
HO
OH
LXXVIII
(CH₃CO)₂O
COCH₃
CH₃COO
3
5
6
HO
OCOCH₃
LXXXII
3(β),6(β)-Diacetoxyallopregnan-5-ol-20-one
COCH₃
O
3
5
6
HO
OCOCH₃
LXXXIV
6(β)-Acetoxyallopregnan-5-ol-3,20-dione
HCl
COCH₃
O
3
4
5
6
OCOCH₃
LXXXV
6(β)-Acetoxyprogesterone

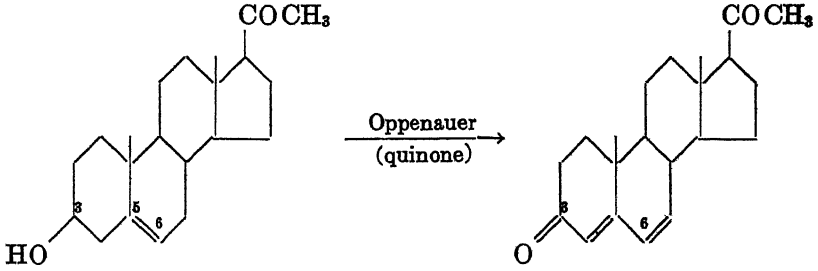
represent a very active progestational compound. It should be emphasized that the over-all yield of this procedure for the preparation of 10-norprogesterone is very small.

In the remaining part of this review some oxygenated progesterones and dehydroprogesterones will be discussed. Progesterones hydroxylated in position 21 will be omitted, however, because compounds of this type belong to the series of the adrenal cortical hormones. As is known, some of the adrenal cortical hormones, e.g., desoxycorticosterone, produce slight progestational action (42).

6-Oxoprogesterone (LXXXI) was prepared by Ehrenstein (7, 9). Hydroxylation of pregnenolone (III) by means of hydrogen peroxide or osmic acid yields two triols, LXXVIII and LXXIX, respectively, which differ in their configuration at carbon atom 6. Oxidation of these different triols with chromic acid leads to an identical allopregnan-5-ol-3,6,20-trione (LXXX), which by dehydration was transformed into 6-oxoprogesterone (LXXXI). The progestational activity of this compound is less than one-fifth that of progesterone. On the other hand, a slight estrogenic effect has been recorded (7).

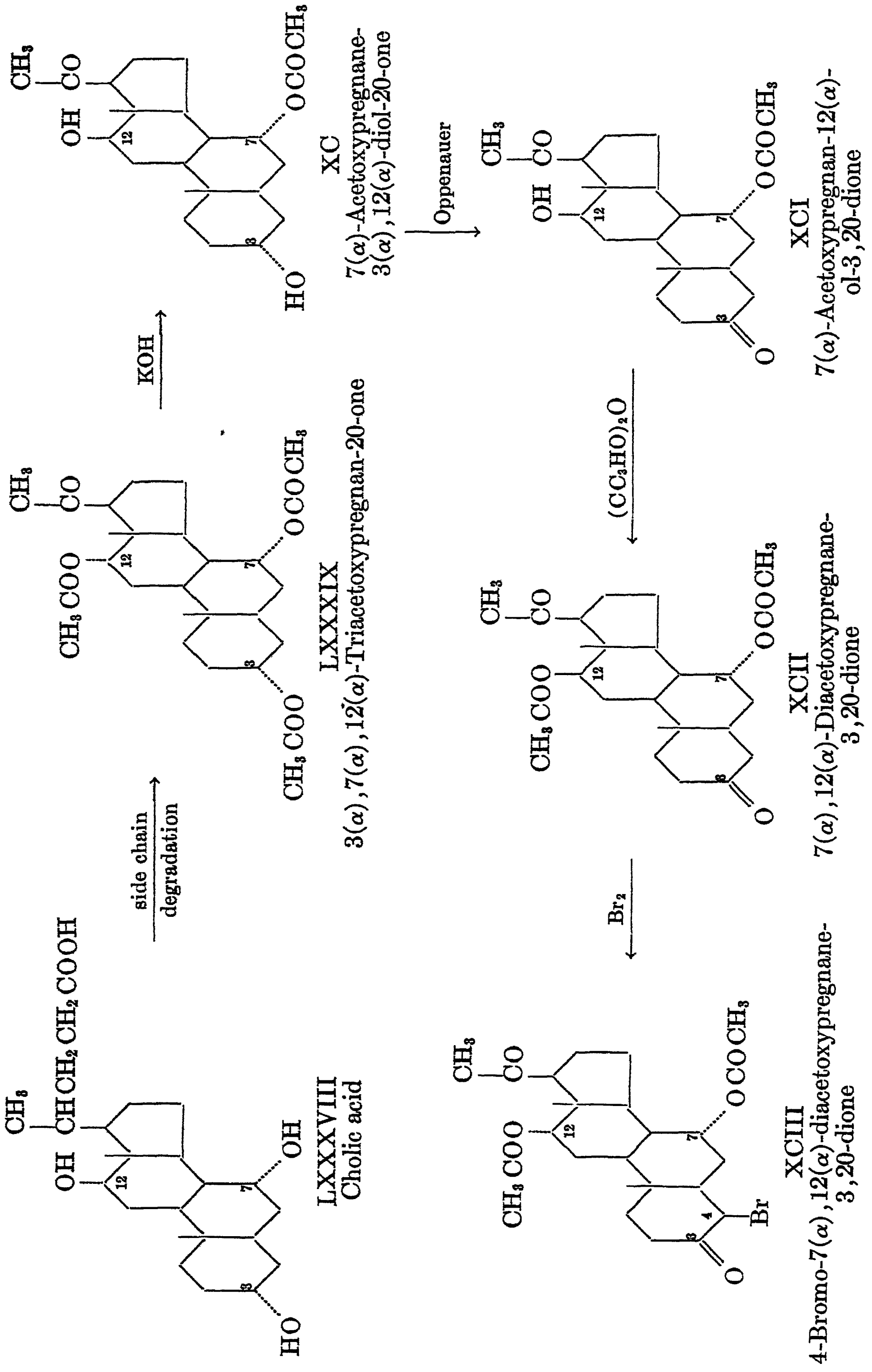
Two methods of preparing the acetate of 6(β)-hydroxyprogesterone (LXXXV) have been described (9, 10, 12). Acetylation of the triol LXXVIII furnished the diacetate LXXXII, which by partial saponification yielded the monoacetate LXXXIII. Partial saponification is usually a rather unsatisfactory procedure. Hence the preparation of the monacetate LXXXIII was later simplified by transforming pregnenolone (III) into the α-oxide (LXXXVI) and subjecting the latter to acetolysis. Oxidation of the monoacetate LXXXIII yielded compound LXXXIV, which by dehydration was transformed into the acetate of 6(β)-hydroxyprogesterone (LXXXV). This compound, tested in two different laboratories (G. W. Corner, A. W. Makepeace), was found to possess one-fifth to one-third the activity of progesterone.

6-Dehydroprogesterone (LXXXVII) was prepared by Wettstein (47). Pregnenolone (III) was subjected to the Oppenauer procedure with the modification of using quinone as hydrogen acceptor. Under such vigorous conditions there takes place not merely a dehydrogenation of the secondary alcohol group, but also the introduction of another double bond. No yields of this reaction are stated. The physiological activity of 6-dehydroprogesterone (LXXXVII) is about one-third to one-half that of progesterone.



III
Δ⁵-Pregnen-3(β)-ol-20-one

LXXXVII
6-Dehydroprogesterone



LXXXVIII
Cholic acid

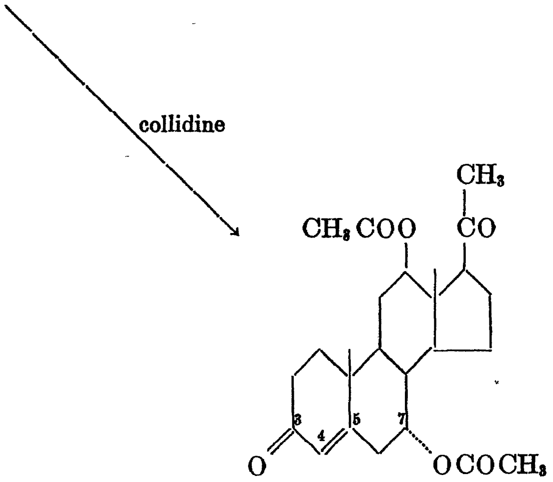
LXXXIX
$3(\alpha),7(\alpha),12(\alpha)$-Triacetoxypregnan-20-one

XC
$7(\alpha)$-Acetoxypregnane-$3(\alpha),12(\alpha)$-diol-20-one

XCI
$7(\alpha)$-Acetoxypregnan-$12(\alpha)$-ol-3,20-dione

XCII
$7(\alpha),12(\alpha)$-Diacetoxypregnane-3,20-dione

XCIII
4-Bromo-$7(\alpha),12(\alpha)$-diacetoxypregnane-3,20-dione



XCIV
7(α),12(α)-Diacetoxyprogesterone

The diacetate of 7(α),12(α)-dihydroxyprogesterone (XCIV) was prepared by Ehrenstein and Stevens (9, 11) by a procedure starting with cholic acid (LXXXVIII). A side-chain degradation involving many steps yielded 3(α),7(α),12(α)-triacetoxypregnan-20-one (LXXXIX), a compound which is now much more easily available by means of Miescher's new degradation method (27, 28). It was partially saponified to compound XC.[6] Subsequent Oppenauer dehydrogenation is selective in that only the hydroxyl group at carbon atom 3 is involved. Hence compound XCI[6] resulted, which by acetylation was transformed into the diacetate XCII. Subsequent bromination yielded the impure bromo compound XCIII, which by dehydrobromination was transformed into the diacetate of 7(α),12(α)-dihydroxyprogesterone (XCIV). The end product was obviously not quite pure. Owing to lack of sufficient material it could not be tested physiologically.

11-Oxoprogesterone (C) and 11(β)-hydroxyprogesterone (XCIX) were prepared by Reichstein and Fuchs (38). When corticosterone (XCV) was treated with toluenesulfonyl chloride in pyridine, the toluenesulfonate XCVI was obtained, which partly reacted with the pyridine hydrochloride to form the 21-chloro compound (XCVII). The mixture of these two substances when treated with sodium iodide furnished the 21-iodo compound (XCVIII), which was reduced with zinc and acetic acid to 11(β)-hydroxyprogesterone (XCIX). This compound was found to have less than one-sixth the activity of progesterone. Treating 11(β)-hydroxyprogesterone (XCIX) with chromic acid furnished 11-oxoprogesterone (C), the physiological activity of which is unknown.[7] Recently Wettstein and Meystre (51) described the transformation of desoxycholic acid into 11-oxoprogesterone, a procedure which required eighteen different chemical steps.

By boiling 11(β)-hydroxyprogesterone (XCIX) with glacial acetic acid and concentrated hydrochloric acid Shoppee and Reichstein (43; *cf.* also 18) obtained a yield of about 65 per cent of 9-dehydroprogesterone (CI). Four milligrams of this substance was active in the Corner–Allen test.

11-Dehydroprogesterone (CIV) was prepared from 12(α)-hydroxyprogesterone (CII) by Hegner and Reichstein (18). 12 (α)-Hydroxyprogesterone in turn was obtained from desoxycholic acid by way of a degradation of the side chain and further transformations of the resulting methyl ketone (2). It (CII) is said to possess no appreciable progestational activity (13). To prepare the 11-dehydro compound, 12(α)-hydroxyprogesterone (CII) was benzoylated and the benzoate (CIII) subjected to a thermal decomposition. 11-Dehydroprogesterone (CIV) produced the Corner–Allen reaction with 2 mg. or less.

17(α)-Hydroxyprogesterone (CV), originally thought to possess the β-configuration, was isolated from adrenal extracts by Pfiffner and North (31, 32) and later also by von Euw and Reichstein (46). It possesses no progestational activity. Prins and Reichstein (37) prepared the same substance by partial

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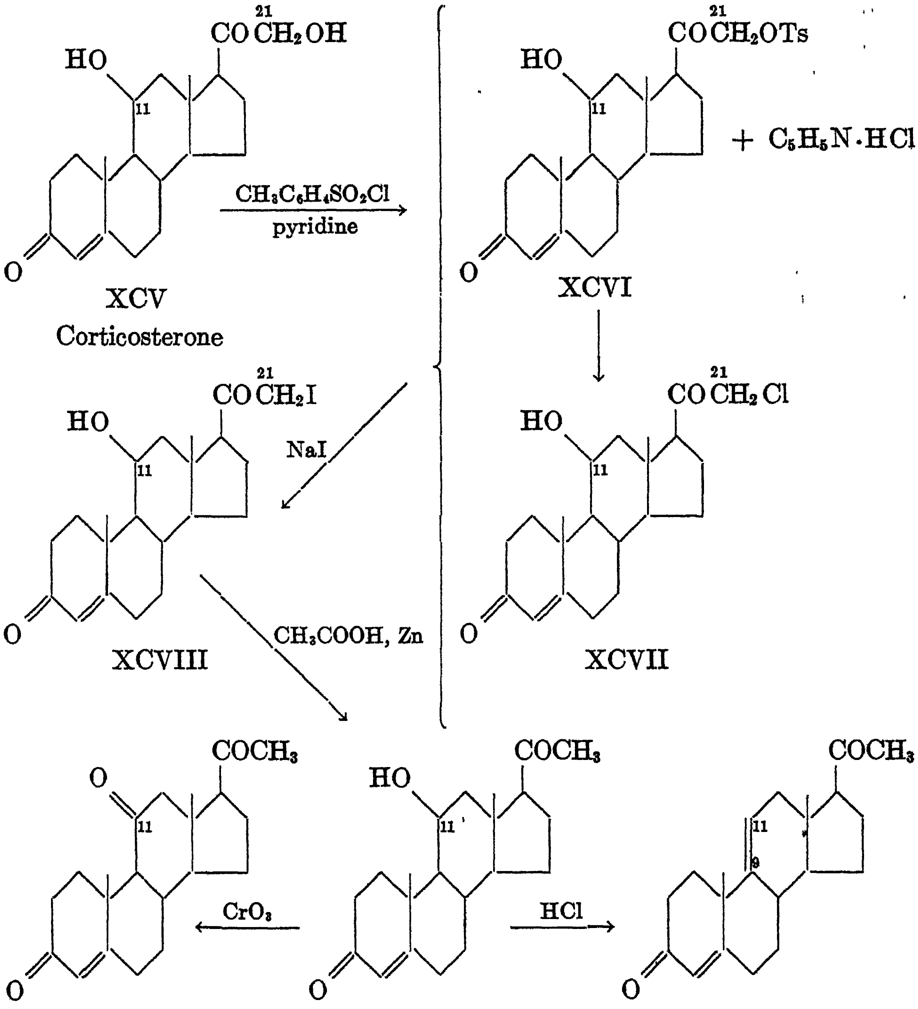
[6] Formulas XC and XCI have been reinterpreted according to Lardon (22); *cf.* also reference 9.

[7] For 11-oxoprogesterone *cf.* also Hegner and Reichstein (19).



XCV
Corticosterone

XCVI

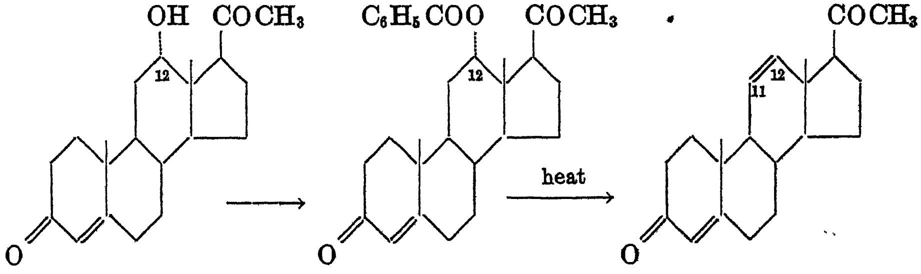
XCVIII

XCVII

C
11-Oxoprogesterone

XCIX
11(β)-Hydroxyprogesterone

CI
9-Dehydroprogesterone



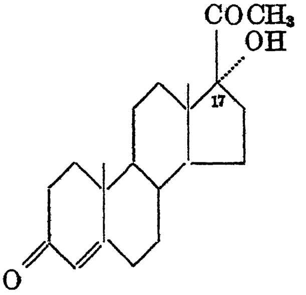
CII
12(α)-Hydroxyprogesterone

CIII

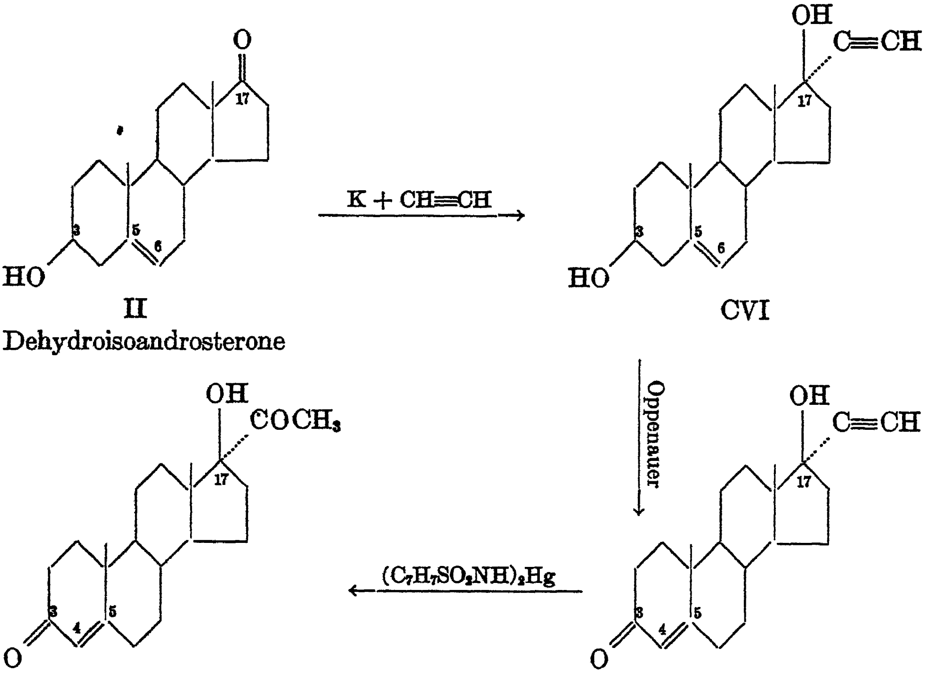
CIV
11-Dehydroprogesterone

synthesis, which will not be reviewed because there are too many steps involved.

The 17(β)-hydroxyprogesterone (CVIII) to which the α-configuration was originally assigned was prepared by Goldberg *et al.* (15) by hydration of ethinyltestosterone (CVII) in the presence of mercuric *p*-toluenesulfonamide. No data are available regarding the physiological activity of this 17(β)-hydroxyprogesterone (CVIII). As is generally known, the intermediate 17-ethinyltestosterone (anhydrohydroxyprogesterone, pregneninolone) (CVII) is an orally effective progestational compound which is accessible from dehydroisoandrosterone (II) (*cf.* 41).



CV
17(α)-Hydroxyprogesterone

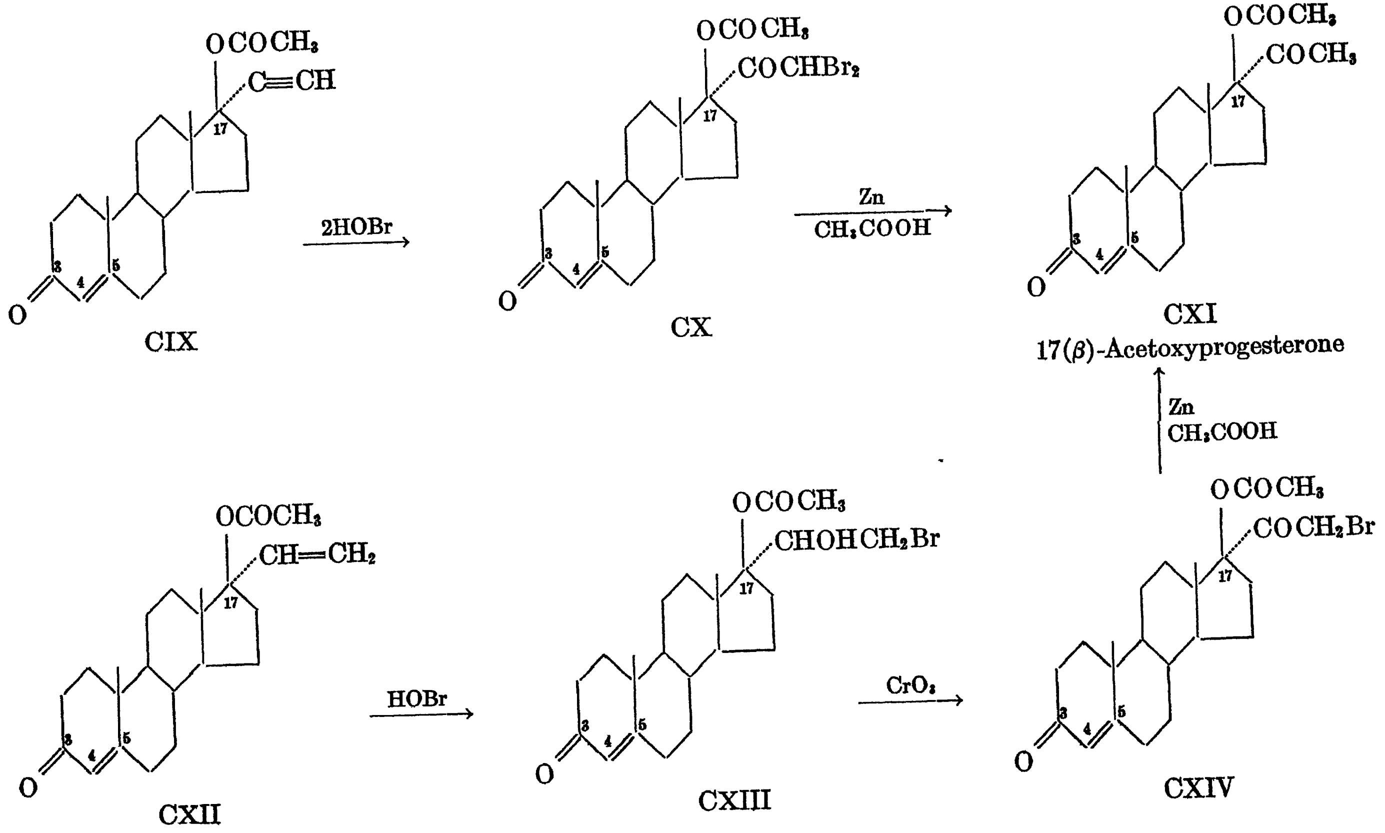


II
Dehydroisoandrosterone

CVI

CVIII
17(β)-Hydroxyprogesterone

CVII
17-Ethinyltestosterone
[anhydrohydroxyprogesterone,
pregneninolone]


OCOCH$_3$
C≡CH
17
3
4
5
O
CIX
2HOBr
OCOCH$_3$
COCHBr$_2$
17
3
4
5
O
CX
Zn
CH$_3$COOH
OCOCH$_3$
COCH$_3$
17
3
4
5
O
CXI
17(β)-Acetoxyprogesterone
Zn
CH$_3$COOH
OCOCH$_3$
CH=CH$_2$
17
3
4
5
O
CXII
HOBr
OCOCH$_3$
CHOHCH$_2$Br
17
3
4
5
O
CXIII
CrO$_3$
OCOCH$_3$
COCH$_2$Br
17
3
4
5
O
CXIV

17(β)-Acetoxyprogesterone (CXI) was first described by Ruzicka (39a, 39b). Recently Salamon and Reichstein (40a) succeeded in preparing this compound from either the acetate of ethinyltestosterone [17(β)-acetoxy-Δ^4-pregnen-20-ine-3-one] (CIX)(39b) or 17(β)-acetoxy-$\Delta^{4,20}$-pregnadien-3-one (CXII) (37a). When reacted with hypobromous acid, compound CIX yielded the dibromo ketone CX, which on treatment with zinc dust in a solution of glacial acetic acid furnished 17(β)-acetoxyprogesterone (CXI). On the other hand, the diene CXII yielded with hypobromous acid the monobromo compound CXIII, which was oxidized by means of chromic acid to the bromodiketone CXIV. On treating the latter with zinc in a solution of glacial acetic acid 17(β)-acetoxyprogesterone (CXI) resulted.

In conclusion it may be stated that of the homologs of progesterone only 10-norprogesterone appears to manifest outstanding progestational activity. Unfortunately it is difficult to prepare. Most of the oxygenated progesterones reviewed produce no significant physiological action. With the exception of 16-dehydroprogesterone all dehydroprogesterones known at present show appreciable progestational activity. They appear to be only slightly less active than progesterone.

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INHIBITION AND RETARDATION OF VINYL POLYMERIZATION[1]

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Ideal inhibitors are defined as substances which cause an induction period in the polymerization of monomers, during which the inhibitor is consumed and after which polymerization starts at its normal rate.

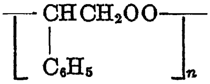
Typical retarders are defined as substances which cause retardation during the entire polymerization, without giving rise to an induction period.

A review is given of the literature concerning the effects of inhibitors and retarders on the uncatalyzed and catalyzed bulk polymerization of various monomers, chiefly styrene. Less information appears to be available concerning the kinetics of catalyzed than of uncatalyzed bulk polymerization in the presence of inhibitors and retarders. It is concluded that both inhibitors and retarders exert their effects by reacting with free radicals produced in the system. Inhibitors react with practically all the free radicals produced, but retarders are less efficient and permit some polymer chains to be initiated. They react with these growing chains and terminate them, thus acting like chain-breakers and reducing the molecular weight of the polymer.

Oxygen exerts opposing effects upon the bulk polymerization of monomers. It reacts with the free radicals initially produced (thermally, photochemically, or catalytically), forming peroxides which are more or less unstable. Depending upon the monomer and the temperature, this peroxide may catalyze polymerization or, if the peroxide is stable, its preferential formation may result in inhibition.

Inihtition and retardation effects in emulsion polymerization are discussed. In general, the effects are comparable to those found in bulk polymerization. In emulsion polymerization "catalysts" are always employed. Owing to the heterogeneous nature of the reaction mixture, it is possible to seperate a retarder (such as 3,5-dinitrobenzoate in alkaline medium) from the locus of chain propagation (the soap micelle), in which the case the retarder hardly affects the molecular weight of the polymer. Evidence is given that in emulsion polymerization with water-soluble "catalysts", activation occurs mainly in the "true" water phase and not in the soap micelle.

Oxygen inhibits the emulsion polymerization at 50°C. of styrene, of butadiene, and of butadiene (75)–styrene (25). In styrene emulsion polymerization a copolymer of styrene and oxygen is formed:



$$\left[-\underset{\displaystyle C_6H_5}{\underset{|}{C}H}CH_2OO-\right]_n$$

It is suggested that this same substance is formed during bulk polymerization of styrene in the presence of oxygen, and is responsible for the catalytic effect of oxygen at high temperatures (80°C. or above). At lower temperatures (55°C. or below) it is fairly stable, and its formation in preference to normal polymerization gives rise to the observed inhibitory effect of oxygen upon the polymerization of styrene at these temperatures.

Brief mention is made of some of the practical aspects of the inhibition and retardation of vinyl polymerization.

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I. INTRODUCTION

Ideal inhibitors are defined as substances which cause an induction period in the polymerization of monomers. During this induction period, the inhibitor is consumed and no normal polymerization occurs. After the induction period, polymerization starts with the normal rate, i.e., the rate which would have been observed in the absence of the inhibitor. If the reaction product formed during the induction period acts as a retarder, the polymerization after the induction period will be retarded.

Typical retarders are defined as substances which cause retardation during the entire polymerization without giving rise to an induction period. If present in large enough quantities, retarders may virtually prevent the initiation of polymerization. If added to a reaction mixture at any degree of polymerization, these substances retard further polymerization. If added in large enough quantities, they virtually stop further polymerization and thus act as "shortstops." Inhibitors can also be used as shortstops.

From a theoretical viewpoint, inhibitors are of special interest. A study of the induction periods produced by ideal inhibitors furnishes a means of measuring the rate at which free radicals are produced in the system, a measurement most difficult to arrive at by any other means. Moreover, the strongest evidence that the polymerization is a chain reaction is the fact that even traces of inhibitors prevent the occurrence of normal polymerization for long intervals.

In the next section is presented a review of the literature concerning the effects of inhibitors and retarders on bulk polymerization, and the interpretation of these effects. This work has dealt mainly with uncatalyzed polymerization, although a few studies have recently been made of peroxide-catalyzed polymerization in the presence of certain inhibitors and retarders.

In Section III, a review is given of similar effects in emulsion polymerizations. This type of polymerization is always catalyzed.

In Section IV, brief mention is made of some of the practical aspects of the inhibition and retardation of vinyl polymerization.

Most of this work has been carried out with styrene, although a few other monomers, notably methyl methacrylate and vinyl acetate, have been used.

II. INHIBITORS AND RETARDERS IN BULK POLYMERIZATION

A. Effect of quinones, nitro compounds, etc.

It has been known for some time that certain substances, particularly quinones and nitro compounds, inhibit or retard the polymerization of vinyl monomers. The existence has been observed of an induction period during which the rate of polymerization is very slow or nil, followed either by an increasing or nearly constant rate of polymerization. The length of this induction period is not always well defined. In other cases, induction periods are not observed, but the polymerization is retarded over its entire course. These effects have been observed in supposedly pure monomers (50), and have been attributed to the presence of traces of certain impurities.

The most comprehensive study yet made of the effect of various substances on vinyl polymerization is that of Foord (20), who observed the effects of a large variety of compounds on the uncatalyzed bulk polymerization of styrene at 60°, 90°, and 120°C. For convenience, these studies were carried out by observing the rate of increase of viscosity of the styrene sample, using a sealed viscometer which served as a reaction vessel as well. The sample was introduced and sealed *in vacuo*, oxygen being thus excluded. Viscosity measurements were made by inverting the vessel and measuring the time required for a definite volume to flow through the orifice. This method is applicable only to the early stage of conversion, but this was the stage that was of most interest. At later stages, the degree of polymerization was measured by alcohol precipitation and weighing of the polymer.

In general, such viscometric procedures are not the best means of following the polymerization process, because the viscosity increases with the molecular weight as well as with the concentration of the polymer. The assumption that the former is constant is not always warranted.

One hundred and thirty compounds were tested. In each case, the induction period (if any) was noted, and the rate of relative viscosity increase over at least the early stages was measured. Results obtained with *p*-benzoquinone at 90°C. are shown in figure 1 and represent the behavior of a typical inhibitor.

The rates of consumption of quinone during the induction period and of polymerization of styrene following the induction period were, in moles per liter per hour:

TEMPERATURE	STYRENE	BENZOQUINONE
°C.		
90	0.117	2.2×10^{-4}
120	0.840	4.2×10^{-3}

We shall return later to these results in discussing the explanation of these effects.

It was observed during these experiments that the yellow color of benzoquinone fades during the induction period and has nearly disappeared at the end of the induction period.

Following the induction period, the rate of polymerization is apparently that of the control, where no quinone was present. In those runs containing the largest quantities of quinone, some retardation of the rate of viscosity increase was observed, but this was thought to be largely due to the fact that the molecular weight of the product was somewhat reduced, and not to a decrease in the rate of conversion. In order to account for the decrease in molecular weight we suggest that a reaction product formed during the induction period retards the polymerization proper. Foord's results are inconclusive in this regard.

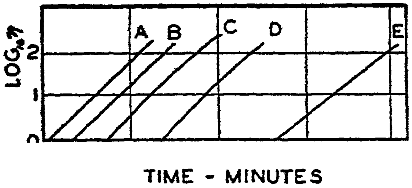


Fig. 1

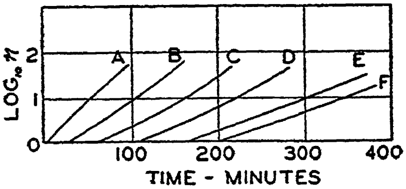


Fig. 2

Fig. 1. Polymerization of styrene at 120°C. in presence of *p*-benzoquinone

	p-BENZOQUINONE	
	Per cent	Millimoles per 100 g. styrene
A	0	
B	0.02	0.185
C	0.05	0.463
D	0.10	0.925
E	0.20	1.850

Fig. 2. Polymerization of styrene at 120°C. in presence of phenanthrenequinone

	PHENANTHRENEQUINONE	
	Per cent	Millimoles per 100 g. styrene
A	0	
B	0.026	0.125
C	0.050	0.240
D	0.120	0.575
E	0.187	0.895
F	0.240	1.15

The lengths of the induction periods increase linearly with the quantity of quinone initially present.

In figure 2 are shown the results obtained with a somewhat less effective inhibitor, phenanthrenequinone. Here it will be observed that the induction periods are still fairly well defined, but that a gradually increasing rate of polymerization is observed, rather than a linear rate.

In addition to substances which behave in this way, which will be referred to as typical or nearly typical *inhibitors*, Foord recognized another class of substances, which produced little or no induction period but retarded the rate of polymerization in varying degrees, the effect continuing throughout the course of the polymerization. These substances will be called *retarders*. Certain substances seemed to have the properties of both classes to some degree.

The following classification of the compounds tried was made by Foord. In arriving at this classification, those substances which acted as retarders were generally tested at 60°C. in a qualitative manner, by noting visually the rate of flow in small sealed tubes at various times.

(*1*) *Accelerators:* These substances increase the rate of polymerization over that observed for pure styrene.

(*2*) No appreciable effect.

(*3*) *Retarders:* Some of these substances also produced short induction periods.

(*4a*) *Inhibitors* giving induction periods of not more than 240 hr. in concentrations of about 1.0 per cent at 60°C., after which the normal rate of polymerization is observed.

(*4b*) *Inhibitors* giving induction periods of at least 600 hr. in 1.0 per cent concentration at 60°C. Only to members of class 4b was the semiquantitative viscometric method described above applied.

The substances tested were classified as follows (omitting classes 1 and 2):

Class 3: Aromatic nitro compounds make up the bulk of this class. Particularly effective are *o*-nitrophenol, 2,4-dinitroaniline, *m*-dinitrobenzene, dinitro-*o*-cresol (location of nitro groups not specified), 2,4-dinitrophenylamine, 2,4-dinitrophenol, 2,4-dinitrophenylhydrazine, 2,4-dinitrotoluene, picric acid, naphthalene picrate, and 1,3,8-trinitronaphthalene. It will be noted that the nitro groups in these substances are in general located in meta positions with respect to each other.

Certain nitroso compounds fall in this class. Most effective is nitroso-β-naphthol. Hydrazobenzene also falls in this group.

Class 4a: 1-Aminoanthraquinone, acenaphthenequinone, benzidine, 2,4-diaminoazobenzene, methylaniline, *p*-phenylenediamine, phenyl-α- and phenyl-β-naphthylamines. Anthraquinone itself is ineffective; 1-aminoanthraquinone probably acts largely by virtue of the amino group. These substances are intermediate in properties between typical inhibitors and retarders.

Class 4b: This class is composed, with the exception of *p*-nitrosodimethylaniline, entirely of quinones of relatively high oxidation potential: *p*-benzoquinone, *p*-toluquinone, phenanthrenequinone, and chloranil.

Hydroquinone and catechol produce some induction period, and the latter also has a retarding effect. Pyrogallol gives strong retardation with little induction period, but phenols in general have a weak effect. Phenol and the cresols are relatively ineffective.

A similar but much less extensive study has been made by Frank and Adams (21), who studied the effect of various inhibitors as 10 per cent solutions in styrene, 3,4-dichlorostyrene, and 5-ethyl-2-vinylpyridine. The last two polymerize more readily than styrene. The temperature was 100°C. They found that picric acid and trinitrobenzene protected the monomers from polymerization for the longest time, 299 hr. for styrene, 39 hr. for the dichlorostyrene, and 120 hr. for the vinylpyridine. The following substances studied are arranged in descending order of effectiveness: 2,5-dihydroxy-1,4-benzoquinone, 1,4-naphthoquinone, 1,4-benzoquinone, chloranil, 9,10-phenanthrenequinone, *tert*-butylcatechol. The following protected the monomers for periods (9 hr.)

not much longer than that observed for the pure styrene control: 4-amino-1-naphthol, hydroquinone, phenyl-β-naphthylamine. Triphenyl phosphite had no effect.

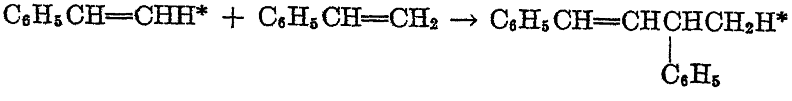
In these experiments no attempt was made to exclude air (oxygen), but approximately the same volume was present in each case. It will be observed that, in general, the compounds found by Foord to be most effective stand high also in the above list, although the experiments were not carried out in such a way as to allow any distinction between inhibitors and retarders to be made.

Since *p*-benzoquinone appears to possess the properties of a typical inhibitor, its effect on vinyl polymerization has been studied by a number of investigators. Breitenbach, Springer, and Horeischy (7) observed that hydroquinone does not stabilize styrene against polymerization in the absence of oxygen, but is very effective when oxygen is present. They believed benzoquinone to be the true inhibitor.

The effect of various quinones on the bulk thermal polymerization of styrene has been studied by Breitenbach and Breitenbach (4) and Breitenbach and Horeischy (5). In contrast to the results obtained by Foord, they claimed that during what Foord called the "induction period" a slow polymerization actually occurs, even in the presence of as much as 2 per cent quinone, leading to a polymer of so low a molecular weight (300–600) that polymerization could not be detected by Foord's viscometric method. They carried their experiments out at temperatures and quinone concentrations comparable to those used by Foord, but determined the polymer formed by volatilizing the unreacted styrene. The quinone disappears during the "induction period" and is partially converted to hydroquinone. Similar results were observed using chloranil. It is evident from their results that the authors were not justified in assuming a polymerization during the induction period. Actually, as will be shown below, their "polymer" is very probably the reaction product of two molecules of styrene with one of quinone.

Using the series of methylated *p*-benzoquinones from monomethyl- to tetramethyl-quinone, they found that the efficiency of the quinones in suppressing polymerization was proportional to their normal potentials. Thus, the strongest oxidant, *p*-benzoquinone itself, gave rise to the smallest rate of "polymerization," whereas with the weakest, tetramethylquinone, the greatest rate was observed. Confusion is caused here by the fact that these authors designate as "polymerization" both the reaction occurring between styrene and a typical inhibitor during the induction period, and the retarded chain propagation caused by the less effective methylated quinones.

It had been previously found by Dimroth (13) that the velocities of dehydrogenation of various reducing agents by these quinones were also proportional to their normal oxidation potentials. Breitenbach and Breitenbach interpreted their results as indicating that the initiation reaction consists in a labilization of a hydrogen atom on a styrene molecule, followed by reaction of this activated molecule with another styrene molecule:



$$C_6H_5CH{=}CHH^* + C_6H_5CH{=}CH_2 \rightarrow C_6H_5CH{=}CH\underset{\substack{|\\ C_6H_5}}{CH}CH_2H^*$$

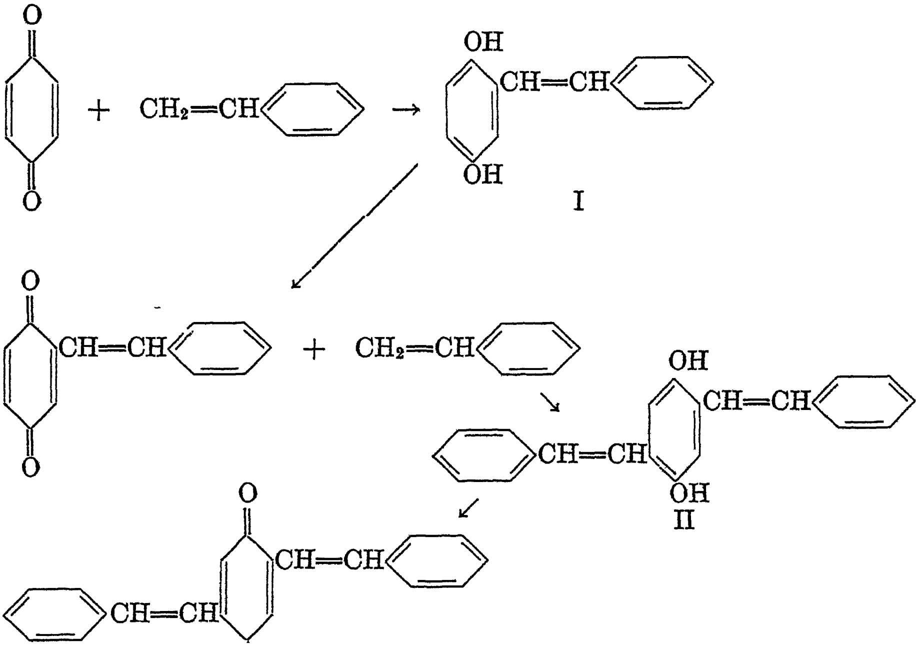
etc. The chain continues until broken by quinone, which abstracts the activated hydrogen atom.

This explanation is deficient in several respects. The nature of the "activation" of the hydrogen atom is not well explained. The peculiar effectiveness of quinones as inhibitors is not explained, since it appears that any strong oxidizing agent might serve equally well. Further, the reason for the effectiveness of several other classes of compounds, notably the aromatic nitro compounds, is not clear. It is especially difficult to explain on this basis the effectiveness of hydrazobenzene, methylaniline, and phenyl-α- and phenyl-β-naphthylamines, although admittedly these substances are not so efficient as the quinones.

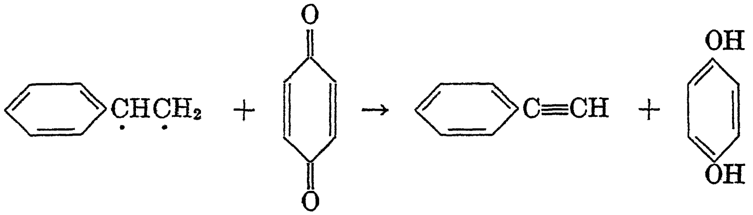
It had been suggested earlier by Springer (58) that polystyrene is first formed and then decomposed by the quinone, but, as pointed out by Foord (20), this suggestion is at once disposed of by the fact that polystyrene in benzene solution suffers no decrease in molecular weight on being heated with quinone.

Schulz (48) has also investigated the effect of *p*-benzoquinone on the thermal polymerization of styrene. The details of this investigation are not available, and the method used for the measurement of polymerization is not known. Schulz concurs with the finding of Foord that quinone produces induction periods, but finds the induction periods to be somewhat less than directly proportional to the initial quinone concentration, indicating that the quinone disappears also by some side reaction.

An attempt has been made by Kern and Feuerstein (29, 30) to identify the actual product formed by the reaction of *p*-benzoquinone with the activated styrene molecules. Reasoning by analogy to the known reactions of quinone with aniline, hydrochloric acid, and aromatic thiols (14), they suggested that reactions of the following type might occur:

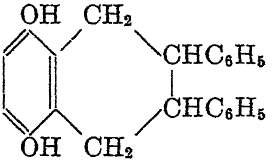


It was also thought possible that the production of hydroquinone might be due to the reaction of an activated styrene molecule with quinone as follows:



This latter reaction does not appear very probable.

Experimentally, it was found that by heating styrene and quinone together in nearly equal mole ratio for several hours at 100–150°C., quinhydrone and hydroquinone are formed, as observed by Breitenbach and Breitenbach (4). In addition, on vacuum distillation of the mixture they obtained a residue which was shown to contain phenols. A product was isolated which gave an elementary analysis corresponding to the suggested structure:

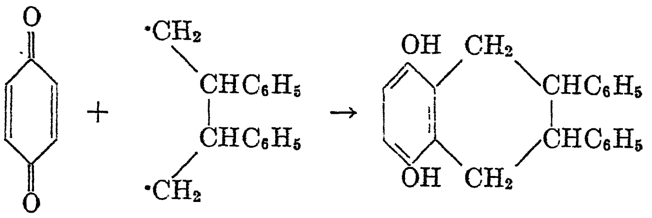


III

On distillation of this substance with zinc dust, a stable hydrocarbon was produced. This hydrocarbon did not react with potassium permanganate, and thus appeared to have no aliphatic unsaturation. They concluded that structure III was probably correct for the reaction product and that I and II were unlikely.

No phenylacetylene was found. The production of hydroquinone was believed to be due to the oxidation of III by the *p*-benzoquinone, with consequent reduction of the latter. Since it is probable that the oxidation potential of III is lower than that of *p*-benzoquinone, this explanation is plausible.

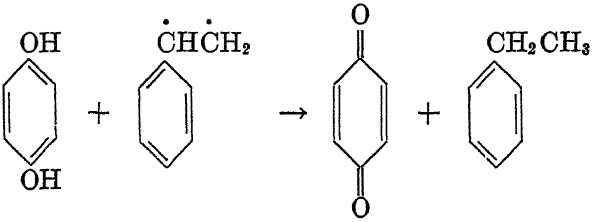
The formation of III was attributed by Kern to the reaction of the styrene dimer diradical with quinone:



III

More will be said later concerning this diradical formulation.

In this connection, it may be well to note the observation of Goldfinger, Naidus, and Mark (22) that on heating equimolar quantities of styrene and hydroquinone for several hours at 150°C. quinone and ethylbenzene are formed, the reaction being formulated as proceeding through the monomer diradical:



It would be expected that the quinone formed would react further with the styrene in the manner postulated by Kern (29), thus producing hydroquinone again. It appears that styrene can react with quinone with the production of hydroquinone, or with hydroquinone to produce quinone. The processes involved are evidently irreversible, and their relative rates do not appear from the present data.

Goldfinger, Skeist, and Mark (23) carried out a study similar to that of Foord (20), using *p*-benzoquinone and styrene at 70°, 100.7°, and 130°C. in the absence of catalyst. They found, as did Foord, that induction periods were observed which were proportional to the initial concentration of quinone. However, the polymerization did not immediately set in with its normal rate (i.e., the rate in the absence of inhibitor) at the end of the induction period. It appeared (the data are sparse and apparently not very precise) that the rate immediately after the induction period was inversely proportional to the initial concentration of quinone.

It was also found that the molecular weight of the polymer formed was inversely proportional to the initial concentration of quinone. Some indication of this fact had also been obtained by Foord. This could be explained by assuming either that the reaction product formed during the induction period has properties of a retarder or that the inhibitor, when in the very small concentrations that are present toward the end of the induction period, does not react with all the free radicals before these are able to initiate polymerization. Thus the inhibitor might act at this stage as a retarder. Whether the termination of the growing chains is due to the quinone itself, or whether the quinone has been consumed and the effect is due to the retarding effect of its reaction product with the styrene, cannot be decided from the evidence at hand.

Breitenbach and Schneider (6) have studied the effect of *p*-benzoquinone and of chloranil in the thermal polymerization of styrene. Their purpose was to prepare polymers of such short chain length that their molecular weights could be determined by direct cryoscopic measurements. The values thus obtained were to be used to check Staudinger's viscosity relationship. They found that *p*-benzoquinone was too reactive and disappeared too rapidly by side reactions to serve their purpose. Chloranil was found to be more suitable. In its presence, polymers were obtained whose molecular weights from cryoscopic measurements were 360–600 (*cf.* Breitenbach and Breitenbach (4)). The chlorine analysis indicated that there was probably more than one molecule of chloranil in each "polystyrene" molecule. Thus, the chloranil had apparently entered the chain, indicating that the radical formed by reaction of chloranil with a growing chain was still capable of propagating the chain. However, it appears that this conclusion must be received with considerable reservation. These authors found the apparent molecular weight of their "polymers" to vary widely with the solvent employed, being ten times lower in dibromocamphane than in benzene. The explanation of this effect is not established. Also, it is not certain that the "polymer" was freed from unreacted chloranil. The "polymer" was stated to be a brown, sticky mass which was soluble in methanol. Again, the term "polymer" may not be a correct description of this reaction product. (See above discussion of the work of Breitenbach and Breitenbach (4)).

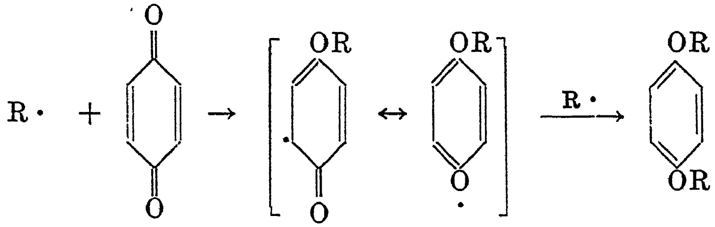
The effect of chloranil has also been studied by Price (43, 47), who found that the chloranil entered into the polymer, but apparently only in the proportion of one chloranil residue per polystyrene molecule. In carrying out this experiment 5 g. of benzoyl peroxide, 4 g. of chloranil, and 25 ml. of styrene were heated at 100°C. for an interval of time not stated. Since the yield of polymer was 15.7 g., it was stated that chloranil did not act as a retarder.

In establishing the molecular weight of the product formed, use was made of the solution viscosity relationship put forward for polystyrene of low molecular weight by Kemp and Peters (28). Since this relationship probably gives results that are much too low (1, 44, 16), it is probable that the true molecular weight found for the polymer prepared in the presence of chloranil is considerably higher than the reported value of 1300. This makes it appear that several chloranil residues must be present in each polystyrene molecule, provided it is certain that the polymer is free of unreacted chloranil. In this experiment it appears from blank runs that this was the case. It is emphasized that Price's experiments were carried out with unusually large concentrations of benzoyl peroxide and chloranil. Evidently, under these circumstances chloranil does not behave like a typical inhibitor. Kinetic studies are needed to decide this point. 3,6-Dichloroquinone was found to behave in the same way as chloranil.

Cohen (9) has recently studied the polymerization of 3.46 molar styrene in benzene at 64° and 74°C. in the presence of 0.0208 to 0.0714 molar benzoyl peroxide and 0.00444 to 0.00463 molar benzoquinone. Rates of polymerization were followed by methanol precipitation of the polymer. It was stated that if polymer had been determined by evaporation of the volatile material, residues would probably have been found quite early in the reaction. However, the nature of the product formed during the induction period was not established, and it can only be concluded that if it was polymeric in nature, its molecular weight must have been very low.

It was found by Cohen that induction periods were produced by quinone, as in thermal polymerization. These induction periods were approximately inversely proportional to the initial concentration of benzoyl peroxide, although the kinetics were complicated by the fact that the presence of quinone accelerated the decomposition of the benzoyl peroxide. Approximately equal molar quantities of quinone and peroxide were consumed during the induction period. The end of the induction period was not sharply defined, but instead a period of retarded rate was observed before the final linear rate was reached.

It was believed that the monomer free radicals react with quinone largely to produce diethers of hydroquinone, rather than to produce quinones or substances having free hydroxyls, since it was found that substances such as hydroquinone diethyl ether and diacetate had little or no retarding effect, whereas 2,5-di-*tert*-butylhydroquinone and 2,5-di-*tert*-butylquinone (which may be regarded as analogous to the compounds which would be produced by addition of radicals to the carbon–carbon double bond of the quinone) retarded polymerization more strongly than was actually observed after the induction period:



Melville and Watson (39) have found that whereas *p*-benzoquinone completely inhibited the thermal bulk polymerization of styrene and methyl methacrylate, when benzoyl peroxide was employed with these same monomers, *p*-benzoquinone produced no induction period but rather a retarded polymerization. The details of the experiments in which benzoyl peroxide was employed are not at present available, and it is therefore impossible to say whether or not these results actually conflict with those of Cohen.

The retardation of styrene polymerization by nitro compounds has been studied by Price, subsequent to the work of Foord (20). Price, Kell, and Krebs (46) observed that *m*- and *p*-nitrobenzoyl peroxides not only failed to initiate polymerization of styrene but actually stabilized it at temperatures at which thermal polymerization would normally have been appreciable. Price and Durham (45) studied the effect of nitrobenzene, 2,4-dinitrochlorobenzene, and nitromethane. In this work, benzoyl peroxide was employed as initiator, and rather large quantities of the nitro compounds were employed—for example, 5 g. of 2,4-dinitrochlorobenzene or 3 ml. of nitrobenzene per 25 ml. of styrene. Molecular weights and analytical evidence were presented tending to show that one retarder residue was present in each polystyrene molecule, but the molecular weight measurements are open to the same doubt as mentioned above.

Nitromethane was found to have no retarding effect, and in fact could be employed as a solvent in carying out the polymerization. Thus it appears that the nitro group must be on a benzene ring to be effective.

Price (43) has also found that α-nitrothiophene acts as a retarder and reduces the molecular weight of the polymer. Again, it was believed that one nitrothiophene residue was present in each polystyrene molecule.

B. *Effect of oxygen*

The effect of oxygen on the polymerization of vinyl compounds has been such a vexed question as to deserve separate treatment from the compounds which have been grouped together in the preceding discussion. Oxygen has been found to exert a catalytic and an inhibitory effect, depending upon the monomer and the conditions employed.

Simon (53) first observed that the polymerization of styrene is accelerated by heat and by air. Stobbe and Posnjak (57) observed that samples of styrene which had been stored for several days at room temperature in the presence of oxygen polymerized much more rapidly at 200°C. than freshly distilled samples. They supposed that a catalyst was formed by the interaction of styrene and oxygen during storage, but did not investigate its nature. It was observed that the sample stored for 14 days polymerized immediately and rapidly, but that the other, after an induction period of about 7 hr., also polymerized quite rapidly, although not so rapidly as the stored sample. The temperature employed in this investigation was very high, and it does not appear that this induction period can be attributed to oxygen, in view of the results obtained by Medvedev and Zeitlin (37) which we shall discuss below. Possibly the catalyst formed during the 14-day period of storage destroyed some unknown inhibitor present in the monomer, while the 7-hr. induction period corresponded to the time necessary to destroy this inhibitor at 200°C.

Taylor and Vernon (59) studied the effect of oxygen on the photopolymerization of styrene and vinyl acetate. They allowed solutions of the monomers in ethylbenzene and ethyl acetate, respectively, to stand in contact with pure hydrogen and pure oxygen at room temperature for periods up to 144 hr., and then submitted the samples to photopolymerization at 100°C. They found that storage in oxygen accelerated the photopolymerization of styrene and produced no induction period. Photopolymerization occurred at an appreciable rate in the oxygen-free sample also. In the case of vinyl acetate, on the other hand, storage in oxygen resulted in a markedly decreased rate of polymerization.

Staudinger and Schwalbach (56) found that the thermal polymerization of vinyl acetate is accelerated by oxygen, without which no appreciable reaction occurs under 180°C. They confirmed the findings of Taylor and Vernon (59) for the photopolymerization, observing that whereas in an inert atmosphere the photopolymerization of vinyl acetate was nearly complete at room temperature in 6–12 hr. under their conditions, in the presence of air no change was observed after 6 hr., and only a small quantity of polymer was produced in 12 hr. They suggested that at low temperatures the activated styrene molecules formed by absorption of light quanta are removed by the formation of an inactive peroxide, whereas at high temperatures (absence of light) the peroxide formed is active and can initiate polymerization. However, in neither case could they find detectable quantities of peroxides.

It was found by Staudinger and Lautenschlager (55) that the polymerization of styrene at 80°C. (in the absence of added catalysts) is 2.5–3 times faster in the presence of oxygen than in its absence. They stated, on the basis of this experiment, that peroxide catalysts function only through the release of molecular oxygen. This view, however, was entirely disproved by Houtz and Adkins (27), who showed that oxygen was a much less effective catalyst for the polymerization of styrene at 100°C. than an equivalent molar quantity of benzoyl peroxide or diisobutylene peroxide, and that furthermore the latter yielded only a trace of molecular oxygen on thermal decomposition. Oxygen is certainly therefore not to be regarded as a direct catalyst for vinyl polymerization.

Thompson and Burk (60) studied the polymerization of styrene at 118°C. in the presence and absence of oxygen, and found that oxygen produced an induction period of about 30 min., after which polymerization proceeded more rapidly than in its absence. They found that very highly purified styrene polymerized *in vacuo* at a measurable rate (although slower than in the presence of oxygen), and thus were really unable to prove their contention that thermal polymerization of styrene probably does not occur, and that polymerization, at least that of styrene, is always to be attributed to traces of catalysts. We shall return to this question in Section C.

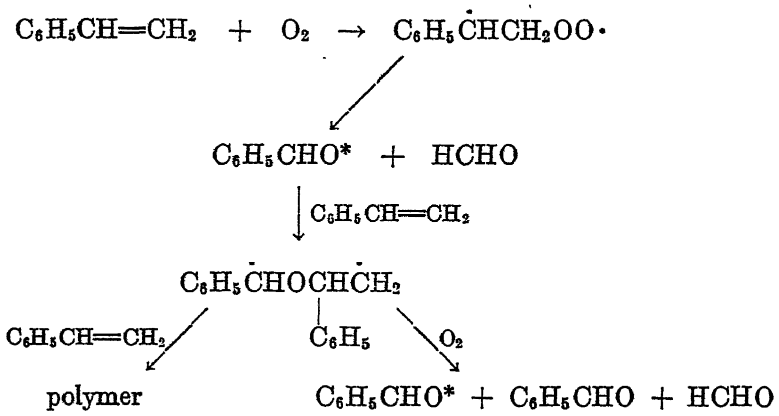
The effect of oxygen on the polymerization of methyl methacrylate has been studied by workers at E. I. du Pont de Nemours and Co. (15) (names not given). In the absence of light and oxygen, bulk polymerization of very pure methyl methacrylate was found to be exceedingly slow at 65°C., but proceeded at an appreciable rate at 170°C. and 210°C. With 0.01 atm. of oxygen (no agitation) polymerization at 65°C. was markedly acclerated, and in 0.1 atm. was faster yet. However, the photopolymerization at 35°C. was slower with 1 atm. of oxygen than with 0.1 atm., although faster in both cases than in the absence of oxygen. These results appear to indicate definitely that oxygen exerts competing effects, and destroys as well as generates active centers.

Melville (38) has found that the initial vapor-phase photopolymerization of methyl methacrylate is inhibited by traces of oxygen, although if solid polymer is once formed on the walls of the vessel, it was found that its continued growth was not retarded by the presence of several hundred millimeters of oxygen pressure.

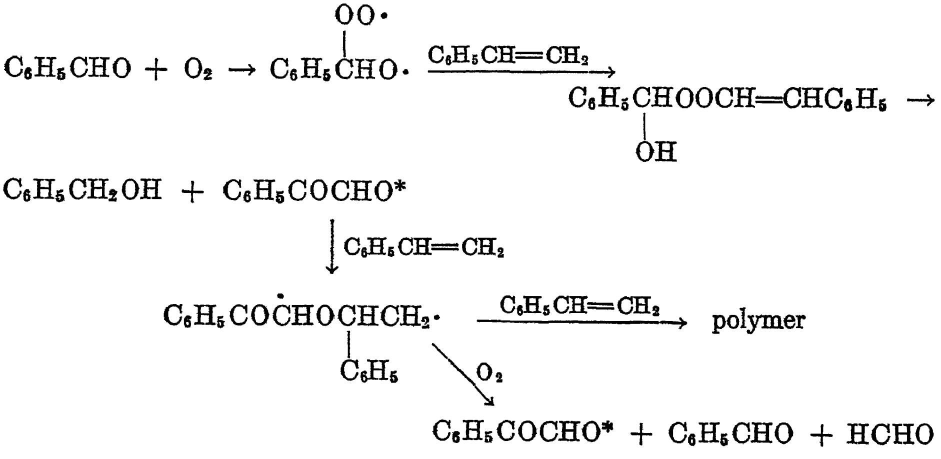
Barnes (2), studying the photopolymerization and thermal polymerization of vinyl acetate and methyl methacrylate in sealed tubes at 0°C., found that polymerization was completely inhibited in the presence of 1 atm. of oxygen, thus confirming the findings of Staudinger and Schwalbach (56) and Taylor and Vernon (59). In the case of methyl methacrylate, Barnes found that thermal polymerization at 65°C. is nearly completely inhibited by oxygen. This result is contradictory to that found by the du Pont workers (15). In neither study was the sample agitated while in contact with oxygen. Barnes explained this inhibitory effect as due to preferential reaction of the active centers produced by irradiation with oxygen to form peroxides, rather than with monomer to form polymer. The peroxides thus formed may also initiate active centers, but these also react preferentially with oxygen. Peroxides were detected experimentally. Their rate of formation in methyl methacrylate exposed to air at 27°C. was much faster when the sample was irradiated than when it was in the dark.

It was also found that the benzoyl peroxide-initiated polymerization of methyl methacrylate was retarded by the presence of oxygen.

Medvedev and Zeitlin (37) have studied the reaction of oxygen with styrene at 80°C. under conditions of very effective agitation, such that the liquid phase was always saturated with oxygen. They found no evidence of inhibition, but rather an acceleration of the polymerization. About 2.5 times as much styrene disappeared, with formation of benzaldehyde and formaldehyde (the amounts of which accounted nearly completely for the absorbed oxygen), as disappeared to form polymer. Further, they found no appreciable quantities of peroxide to be formed—at least so far as the acid potassium iodide test could detect. They concluded that if a peroxide were initially formed, which they conceded appeared very likely, it was immediately decomposed by reaction with the monomer to produce an active center which might then be oxidized further or react with monomer to form polymer:



In addition, they found that benzaldehyde had a pronounced accelerating effect on the oxidation–polymerization rate, and concluded that it also reacted with oxygen to form a labile peroxide which initiated another series of chain reactions:



The accumulation of benzaldehyde was thus believed to be the cause of the observed autocatalytic form of both the oxidation and polymer-formation curves.

It will be noted that in this rather elaborate scheme the formation of an initial active center by thermal activation, followed by reaction with oxygen or monomer, does not play a part. The active center is formed only by reaction of inactive styrene (or benzaldehyde) with oxygen. This recalls the view of Staudinger (55), who regarded molecular oxygen as a catalyst itself.

Although they did not analyze the polymer formed to see whether it contained oxygen—in particular, peroxide oxygen—it was found that it had no catalytic activity when added initially to a reaction mixture. Staudinger and Lautenschlager (55) found that polystyrene prepared in the presence of oxygen contained appreciable amounts of oxygen, but did not give a peroxide test. In the discussion of the inhibition of the emulsion polymerization of styrene, we shall see that a polymeric styrene peroxide is formed in that case also.

Kharasch and Nudenberg (31) have recently observed that at a temperature of 55°C. oxygen acts as an effective inhibitor for the bulk polymerization of styrene.

C. Nature of the inhibition process

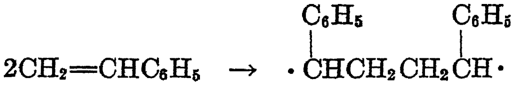
In the previous discussion we have described inhibitory effects produced by several substances upon vinyl polymerization, in particular, the polymerization of styrene. At certain points, we have anticipated somewhat the discussion of this section in presenting the explanations of the authors for the phenomena observed. We shall now try to propose a general scheme for the explanation of these effects. On certain important points no definite decision can be made, and these points must be left for future experiments to decide.

Of the kinetic studies which have been made of the effect of inhibitors and retarders on the bulk or solution polymerization of vinyl monomers, all but one (9) have dealt with either the photopolymerization or the thermal polymerization. At least, in those reactions which have been termed "thermal," no catalyst has been deliberately added. However, the important question remains whether the formation of active centers in these cases is due to a true thermal reaction or to initiation by traces of catalytic impurities, probably peroxides. It may well be imagined that the nature of the active centers which react with the inhibiting substances will depend upon the mode of activation.

Staudinger and Schwalbach (56) called attention to their difficulties in obtaining vinyl acetate sufficiently free of peroxides not to polymerize appreciably in an inert atmosphere. Conant and Tongberg (10), working at high pressure with vinyl acetate, decided that in this case the presence of peroxide catalysts was not essential, but that true thermal polymerization occurred, accelerated by the high pressure. With isoprene, they found that the pressure polymerization was not noticeably faster with a sample that had been shaken with oxygen for several hours than with a freshly distilled sample. However, Conant later found (11) that even the freshly distilled sample was not free of oxygen, since on storage with triphenylmethyl the rate of polymerization was reduced to one-tenth of that of the untreated sample. By no device were they able to prepare isoprene in so pure a state that it failed entirely to polymerize under their conditions. Thus it appears that uncatalyzed polymerization may be possible, at least at high pressures.

Cuthbertson, Gee, and Rideal (12) found that carefully purified vinyl acetate was very resistant to polymerization.

Moureu and Dufraisse (40), who were the first to show that traces of peroxides and not oxygen itself were responsible for the air-induced polymerization of vinyl compounds (acrolein in the above paper), were strongly of the opinion that vinyl polymerization is never induced by the spontaneous thermal generation of active centers, even in the purest monomers that care and ingenuity can produce. A similar view has been expressed by Norrish and Brookman (41). Such a contention is, of course, difficult to disprove, but it is apparently believed by most workers in this field (for example, Mayo (35a, 36), Schulz (52), and Walling, Briggs, and Mayo (62)) that true thermal polymerization is possible, at least in the case of styrene and probably also in the case of methyl methacrylate (61). The kinetic studies carried out by these authors have indicated that thermal initiation occurs as a second-order reaction of two styrene molecules, presumably to form a dimeric radical. We have already seen that a similar diradical (but differing in the location of the phenyl groups) has been suggested by Kern and Feuerstein (29, 30) to account for the addition product of two styrene residues with quinone observed on heating these substances together:



$$2CH_2{=}CHC_6H_5 \rightarrow \cdot\overset{C_6H_5}{\overset{|}{C}}HCH_2CH_2\overset{C_6H_5}{\overset{|}{C}}H\cdot$$

Activation of the double bond of vinyl compounds has been represented by Harman and Eyring (24) as proceeding by either of two mechanisms:

(*a*) By a rotational adiabatic (i.e., without change of electronic energy) transition from the singlet ground state (π electrons have opposite spins) to an upper singlet state, in which the electrons' spins are still opposed. This transition requires 40,000 cal. and is concerned in ionic polymerization, Friedel–Crafts reactions, etc.

(*b*) By a transition from the singlet ground state (π electrons have opposite spins) to a triplet state in which the spins of the electrons are the same. This transition requires only 25,000 cal., but the frequency factor (i.e., the probability of transition) is much lower than for mechanism (*a*). This is the mechanism concerned in the thermal and peroxide-initiated polymerization of vinyl compounds. (In both mechanisms, the products have the activity of free radicals.) Whether the monomer diradical formed then reacts with another molecule of styrene to produce a dimer diradical is not discussed by Harman and Eyring.

The probability of transition by mechanism (*b*) is increased by the presence of strong inhomogeneous magnetic fields, such as those present in aryloxy and acyloxy free radicals, triarylmethyls, etc. Such a free radical attacks the monomer by pairing its electron with the π electron of opposite spin in the monomer, thus producing a monoradical:

$$R\cdot + \underset{\text{Normal}}{C_6H_5CH\underset{\bullet}{\overset{\bullet}{:}}CH_2} \rightarrow \underset{\text{Monoradical}}{C_6H_5\dot{C}H{:}CH_2{:}R}$$

Thus, in thermal polymerization we evidently deal with diradicals, and in catalyzed polymerizations (as by peroxides, diazo compounds, and other free-radical generators) with monoradicals. According to Eyring's view, the activation energy should be about 25,000 cal. regardless of the nature of the catalyst, or whether any catalyst is present at all, provided transitions occur by reaction (*b*). This view appears to be supported by the following data, in which the rate constants for activation of styrene under various conditions are given:

$$K = Ne^{-E/RT}$$

where N is the frequency factor and E is the energy of activation.

	K	REFERENCE
Styrene under nitrogen (supposedly thermal only)....	$1.5 \times 10^{4}e^{-23,300/RT}$	(53)
Styrene with benzoyl peroxide	$10^{10.85}e^{-23,700/RT}$	(52)
Styrene with free radicals....	$10^{12.2}e^{-23,500/RT}$	(50)

From the temperature coefficient of the quinone induction period, Foord (20) obtained a value of 28,000 cal. for thermal activation of styrene.

It should be borne in mind, however, that calculating energies of activation by measurement of the temperature coefficient of the rate is a questionable procedure when such catalysts as benzoyl peroxide are used, since what is actually measured may be the energy of activation for the cleavage of the catalyst itself. Barnett and Vaughan (2a) find that the energy of activation for the decomposition of benzoyl peroxide is from 28 to 32 kcal., depending upon the concentration of the peroxide. Thus, it is questionable whether the constant values of the activation energy tabulated above substantiate Eyring's view.

The question then arises whether substances which inhibit or retard thermal polymerization will react equally readily with the monoradicals produced in catalyzed polymerization. According to the study made by Cohen (9), it appears that they do. Furthermore, it has been found that the catalyzed emulsion polymerization of styrene is inhibited and retarded by the same types of compounds that are effective in bulk polymerization (see Section III).

The reactions of typical inhibitors and retarders can probably be best formulated as follows (illustrated for styrene):

A. Thermal polymerization:

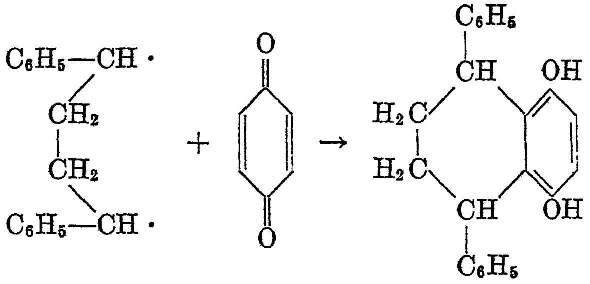
1. Initiation:

$$C_6H_5CH{=}CH_2 \rightarrow C_6H_5\dot{C}HCH_2CH_2\dot{C}HC_6H_5$$

2. Propagation:

$$R\cdot \text{ (either end of diradical)} + C_6H_5CH{=}CH_2 \rightarrow C_6H_5CHCH_2R$$
$$C_6H_5CHCH_2R + C_6H_5CH{=}CH_2 \longrightarrow R(M)_n, \text{ etc.}$$

3a. Termination by inhibitor:



This adduct does not react readily with free radicals, but may have a slight retarding effect.

As we have seen, not all the quinone can be used for termination, as in 3a, since some appears as quinhydrone and hydroquinone. It seems reasonable to interpret the appearance of these products as Kern and Feuerstein (30) have done, as due to reduction of quinone by the substituted hydroquinone produced above.

That all the quinone is not consumed in termination reactions in bulk polymerization is also indicated by the relative rates of quinone disappearance during the induction period and styrene disappearance during subsequent polymerization, as determined by Foord (20). Taking the data for 120°C., Foord calculates the number-average molecular weight of the polymer formed after the induction period to be:

$$\bar{M}_N = \frac{\text{rate of propagation}}{\text{rate of activation}} = \frac{0.84 \times 104}{4.2 \times 10^{-3}} = 20{,}800$$

However, the actual number-average molecular weight is probably greater than 100,000, indicating that we have overestimated the true rate of activation, which is not so large as the rate of quinone disappearance.

The termination reaction is very rapid and occurs almost to the exclusion of the normal propagation reaction. That quinones and aryl nitro compounds react readily with free radicals appears to be indicated by the work of Fieser and Oxford (19) and Fieser, Clapp, and Daudt (18) on the methylation of these substances with lead tetraacetate.

Very recently, Mayo and Gregg (36b) have obtained kinetic evidence tending to indicate that in the thermal polymerization of styrene at 100°C. the adduct produced by the reaction of *p*-benzoquinone with a styrene radical is not inactive, but is capable of continuing the chain, either by copolymerization or by transfer. The rate of disappearance of the quinone is not, therefore, a measure of the rate of activation under these conditions.[2]

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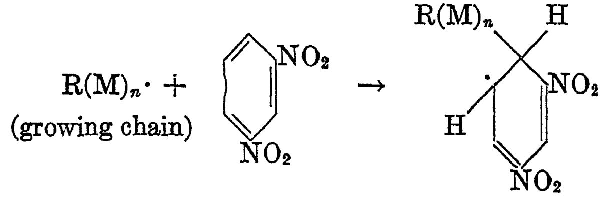
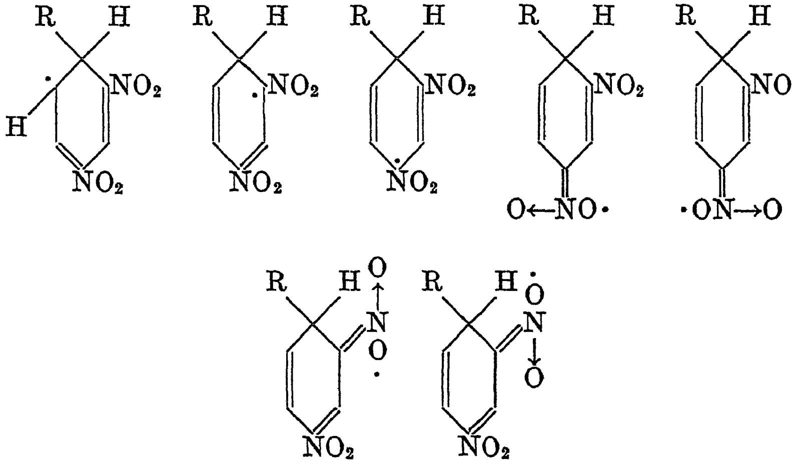
[2] *Note added in proof:* In this laboratory, evidence has also been recently found which indicates that chloranil, and probably *p*-benzoquinone, actually copolymerizes with styrene under certain conditions.

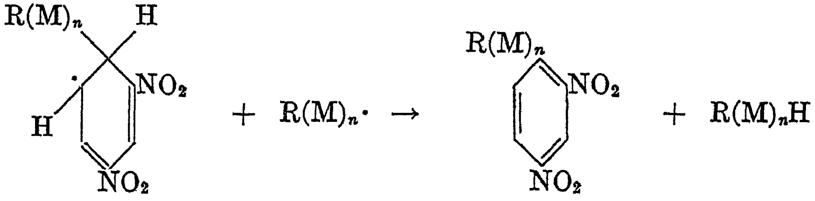
3b. Termination by retarder: The termination reaction of a typical retarder (*m*-dinitrobenzene) can be represented:



The resulting radical is too much stabilized by resonance to propagate the chain at an appreciable rate. This can be readily understood from a consideration of the following resonance forms:



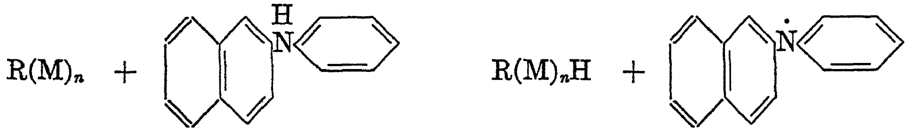
This radical will, however, react with another radical:



as suggested by Price (42, 45).

The reaction of free radicals with retarders such as *m*-dinitrobenzene does not occur so rapidly as with quinone. Therefore, many of the radicals formed are able to propagate chains of some length before reacting with the retarder. Thus, instead of complete or nearly complete absence of polymerization, there is observed instead a retarded rate, leading to a polymer of lower molecular weight than that formed in the absence of a retarder. A similar effect upon the molecular weight is produced by typical chain-transfer agents or modifiers, but since in the presence of these substances a new radical of equal reactivity is produced for each chain terminated, the rate of polymerization is not affected.

In addition, some substances, e.g., those in Foord's class 4a, react less readily with free radicals than typical inhibitors, but more readily than typical retarders. The reaction of such substances as phenyl-α- and phenyl-β-naphthylamines may possibly be explained by reactions such as:



The resulting radical cannot propagate the chain further but may be terminated by reaction with another polymer radical. These amines appear to be intermediate in activity between typical inhibitors and typical retarders.

B. Catalyzed polymerization:

1. Initiation:

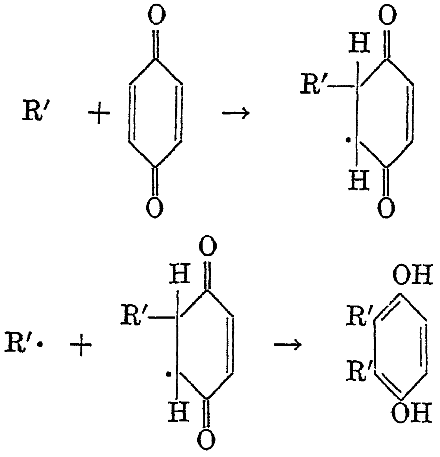
$$R_2 \rightarrow 2R\cdot \quad \text{(dissociation of catalyst)}$$

$$R\cdot + C_6H_5CH{=}CH_2 \rightarrow C_6H_5\underset{\cdot}{C}HCH_2R\text{, designated } R'\cdot$$

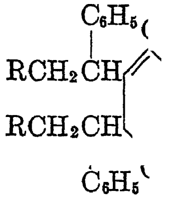
2. Propagation (same as under A):

$$R'\cdot + C_6H_5CH{=}CH_2 \rightarrow\!\!\rightarrow R(M)_n^{\cdot}\text{, etc.}$$

3. Termination by inhibitor:

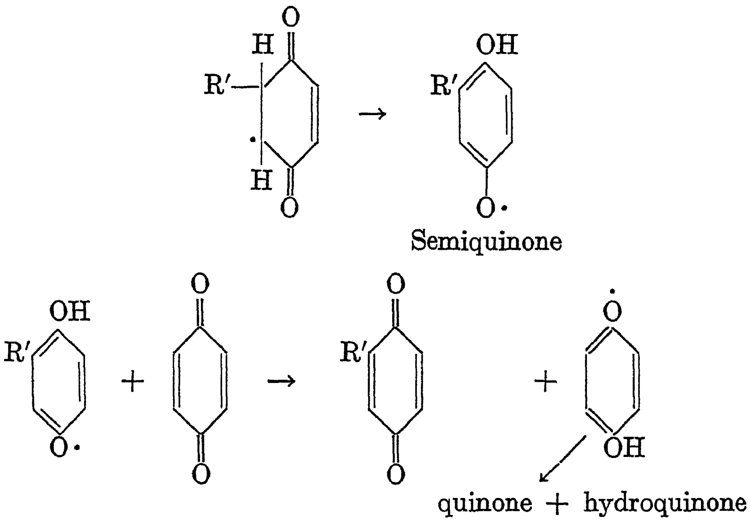


The final product in the case of styrene would evidently be, according to this formulation:



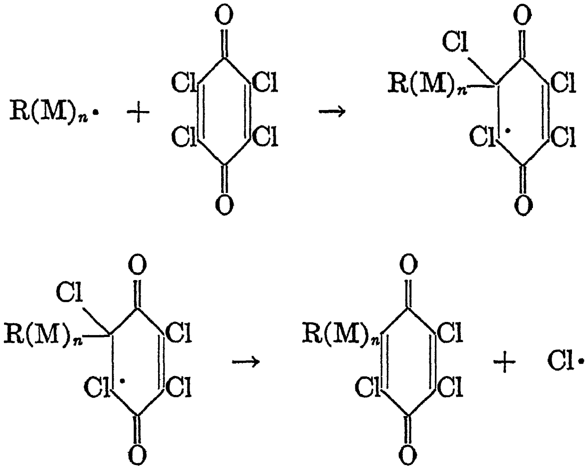
where R represents a fragment of the catalyst. According to Cohen (9) the final product should be represented as an ether of hydroquinone, as we have seen. Present unfinished work carried out in this laboratory tends to substantiate Cohen's formulation.

Price (42) has suggested:



It is also possible that the semiquinone initially formed may lose a hydrogen atom to another R′·, in the same manner as that represented for *m*-dinitrobenzene (page 509).

We have seen that, according to Price (43, 47), chloranil and dichloro-*p*-benzoquinone present the special feature of acting as chain-transfer agents rather than inhibitors. This is supposed to occur as a result of chain initiation by a chlorine atom:



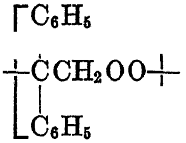
$$Cl\cdot + C_6H_5CH{=}CH_2 \longrightarrow R\cdot$$

This hypothesis cannot be regarded as proved by the experimental evidence, nor is it in agreement with the observations of Foord (20) and of Frank and Adams (21) that chloranil is an effective inhibitor. This apparent contradiction may be caused by the fact that Price used unusually large quantities of benzoyl peroxide as catalyst. In general, a typical chain-transfer agent does not affect the over-all rate of polymerization, although it greatly reduces the molecular weight. This is true only if every free radical formed on termination of one chain initiates another chain. If this condition is not fulfilled, a retarding effect will result.

Oxygen: In the interpretation of the oxygen effects observed in uncatalyzed systems, it should be realized that even at room temperature oxygen reacts slowly with monomers, apparently with the primary formation of peroxides. The rate of this reaction undoubtedly varies with different monomers, and also varies with the temperature. The peroxides formed are more or less unstable and generally decompose at moderate temperatures (50°C. or below), with the formation of compounds which do not act as initiators of polymerization. The rate of polymerization after the induction period will be equal to the normal rate of uncatalyzed polymerization only when all the peroxides formed during the induction period are quantitatively decomposed, with the formation of substances which do not initiate polymerization. The rate of polymerization after the induction period will be in general greater than the "normal" rate if some undecomposed peroxide is still present, but when the rate of thermal or photo-induced formation of free radicals is large in comparison with the rate of formation of free radicals from the residual peroxide formed by reaction with oxygen, the rate of the thermal or photo-induced polymerization of the monomer after the induction period will not be greatly increased by the initial presence of oxygen. In this connection, it is of interest that chloroprene reacts readily with oxygen at room temperature to form a peroxide which is a powerful catalyst for its polymerization (8, 64). Oxygen has no inhibitory effect on this monomer, evidently because the chloroprene peroxide forms free radicals even at room temperature. The behavior of oxygen with chloroprene at room temperature is evidently comparable to that with styrene at 80°C. or higher temperatures.

In Section III it is shown that a polymeric peroxide of styrene is formed during the induction period caused by oxygen in the emulsion polymerization of styrene at 50°C., and that this substance is an effective catalyst for the bulk polymerization of styrene at 80°C. It is reasonable to suppose that this peroxidic polymer is formed also in bulk, and that its breakdown at higher temperatures (above 50–55°C.) is responsible for the accelerating effect of oxygen on the polymerization of styrene at higher temperatures. As we have mentioned, Medvedev and Zeitlin (37) found that the polystyrene produced in bulk at 80°C. in the presence of oxygen had no effect on the polymerization when added initially. However, they purified the polymer by four reprecipitations, as a result of which whatever remained of the polymeric peroxide was probably lost, since this material is of low molecular weight. At 80°C., little peroxide would be expected to remain, since it is unstable at this temperature. It appears probable that the benzaldehyde and formaldehyde found by Medvedev and Zeitlin are decomposition products of the polymeric peroxide.

Although the peroxides formed when oxygen reacts with monomers may not always be polymeric, some instances of such polymeric peroxides are known. Staudinger (54) found that unsymmetrical diphenylethylene formed a peroxide of composition:

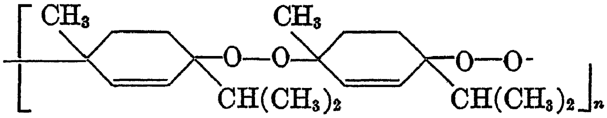


$$\left[-\overset{C_6H_5}{\underset{C_6H_5}{C}}CH_2OO-\right]$$

Staudinger and Lautenschlager (55) isolated polystyrene apparently containing some oxygen but never in a mole-for-mole proportion to the styrene.

Staudinger (54) also isolated a polymeric peroxide of diphenyl ketene.

Farmer (17) reports that when α-terpinene is heated with oxygen, a polymeric peroxide is formed rather than the expected ascaridole:



This substance was observed to be explosively decomposed by heating above 100°C.

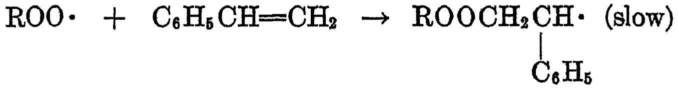
The above considerations may account for the apparently contradictory effects exerted by oxygen under varying conditions, as described in the literature. In general, the following cycle of reactions accounts for the experimental observations; it is presumed in this scheme that the monomer (styrene) is initially free from catalytic impurities.

1. Thermal initiation:

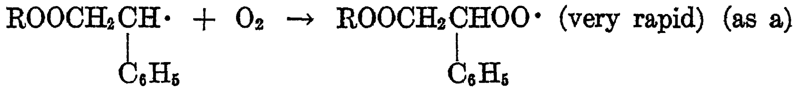
$$2C_6H_5CH{=}CH_2 \rightarrow C_6H_5\underset{\bullet}{C}HCH_2CH_2\underset{\bullet}{C}HC_6H_5 \quad (=R\cdot)$$

2. Peroxide formation:

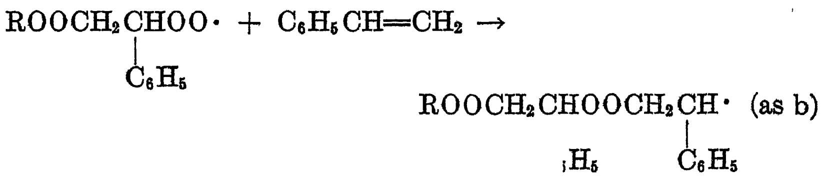
a. $R\cdot + O_2 \rightarrow ROO\cdot$ (very rapid)

b. 

$$ROO\cdot + C_6H_5CH{=}CH_2 \rightarrow ROOCH_2\underset{C_6H_5}{\underset{|}{C}}H\cdot \text{ (slow)}$$

c. 

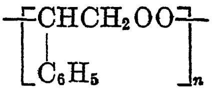
$$ROOCH_2\underset{C_6H_5}{\underset{|}{C}}H\cdot + O_2 \rightarrow ROOCH_2\underset{C_6H_5}{\underset{|}{C}}HOO\cdot \text{ (very rapid) (as a)}$$

d. 

$$ROOCH_2\underset{C_6H_5}{\underset{|}{C}}HOO\cdot + C_6H_5CH{=}CH_2 \rightarrow$$

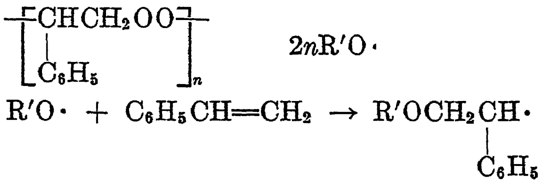
$$ROOCH_2\underset{H_5}{C}HOOCH_2\underset{C_6H_5}{\underset{|}{C}}H\cdot \text{ (as b)}$$

etc., plus termination steps, leading to:



$$\left[\text{—}\underset{\displaystyle C_6H_5}{\underset{|}{CH}}CH_2OO\text{—}\right]_n$$

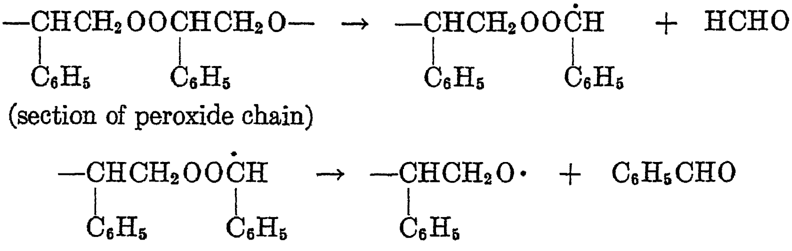
3. Chain initiation by polymeric peroxide:



$$\left[\text{—}\underset{\displaystyle C_6H_5}{\underset{|}{CH}}CH_2OO\text{—}\right]_n \qquad 2nR'O\cdot$$

$$R'O\cdot + C_6H_5CH{=}CH_2 \rightarrow R'OCH_2\underset{\displaystyle C_6H_5}{\underset{|}{CH}}\cdot$$

The peroxide may decompose according to the following series of reactions. Either the R'O· or the carbon radical may serve to initiate further polymerization:



$$\text{—}\underset{\displaystyle C_6H_5}{\underset{|}{CH}}CH_2OO\underset{\displaystyle C_6H_5}{\underset{|}{CH}}CH_2O\text{—} \rightarrow \text{—}\underset{\displaystyle C_6H_5}{\underset{|}{CH}}CH_2OO\underset{\displaystyle C_6H_5}{\underset{|}{\dot{C}H}} + HCHO$$

(section of peroxide chain)

$$\text{—}\underset{\displaystyle C_6H_5}{\underset{|}{CH}}CH_2OO\underset{\displaystyle C_6H_5}{\underset{|}{\dot{C}H}} \rightarrow \text{—}\underset{\displaystyle C_6H_5}{\underset{|}{CH}}CH_2O\cdot + C_6H_5CHO$$

etc.

In this way, the observed oxidation products, formaldehyde and benzaldehyde, may be produced while polymerization is taking place.

4. Normal propagation by thermal radical from 1; this will occur only if this radical escapes reacting with oxygen, which is improbable unless the concentration of oxygen is very small:

$$R\cdot + C_6H_5CH{=}CH_2 \rightarrow C_6H_5\underset{\bullet}{C}HCH_2R$$

These chains may then react with oxygen.

At low temperatures, the polymeric peroxide formed is not cleaved rapidly enough to serve as an effective chain initiator. The stability of the peroxide and the rate of its formation no doubt vary widely with different monomers; probably that of isoprene is among the least stable, while that of styrene is stable at about 50°C. but unstable at 80°C. The chains initiated by other means (e.g., by ultraviolet irradiation) are in effect terminated by reaction 2a, since the radicals react more rapidly with oxygen, which may be regarded as a diradical, than with monomer, resulting in the much less reactive peroxide radical, and the succeeding steps b, c, d, etc. Since the over-all reaction under 2 is much slower than normal polymerization, and yet occurs nearly to the exclusion of normal polymerization, the oxygen is observed to cause nearly ideal inhibition.

At higher temperatures the peroxide breaks down rapidly with formation of initiating radicals, according to 3. Of the radicals thus produced, some will react with oxygen again according to 2, but the polymer peroxide thus formed will again break down with formation of up to $2n$ radicals (n being the average number of peroxide links per polymer molecule) for each initiating radical. From the experiments discussed in section b, it appears that the rate of reaction of these radicals (or those produced thermally from the monomer) with monomer increases much more rapidly with increasing temperature than the rate of their reaction with oxygen. This appears reasonable, since the activation energy for reaction with oxygen is undoubtedly much smaller than that for their reaction with monomer. Thus, as the temperature increases, not all of the many radicals produced react with oxygen, and so the inhibitory mechanism 2 is overpowered by 3, resulting in polymerization even faster than normal polymerization.

III. INHIBITORS AND RETARDERS IN EMULSION POLYMERIZATION

A. Introduction

No studies on the inhibition and retardation of emulsion polymerization proper are to be found in the literature. Related studies on water-solution polymerization have been reported by Hohenstein and Mark (26). In these experiments, a small vessel of styrene was suspended above an aqueous phase containing potassium persulfate and small concentrations of hydroquinone, the whole system being flushed free of oxygen. Styrene vaporized from the small vessel and dissolved in the aqueous phase, where it polymerized. The appearance of a turbidity due to polymer was considerably delayed by the presence of hydroquinone in the aqueous phase. The induction period due to the hydroquinone (quinone under the conditions of the experiment) is considerably shortened by increasing the temperature or by adding emulsifiers. From the temperature coefficient of the induction period a value of about 25,000 cal. was obtained for the energy of activation of the formation of free radicals in the absence of emulsifiers.

Studies on the inhibition and retardation of emulsion polymerization are now being made in this laboratory. These investigations are confined at present to the emulsion polymerization of styrene and of butadiene, and the copolymerization of butadiene (75)–styrene (25). Persulfate has so far been used as "catalyst" in all these studies.

In emulsion polymerizations, "catalysts" are always used to initiate the polymerization. Everything that has been said for bulk polymerization would hold for emulsion polymerization if it were not for the fact that in emulsion polymerizations we are dealing with a heterogeneous system. In general, water-soluble "catalysts" (potassium persulfate, hydrogen peroxide, etc.) are used, these catalysts being completely or nearly completely insoluble in the monomer phase. In emulsion polymerization, the polymer always appears in the aqueous phase and not in the monomer phase. According to Harkins (25), the polymerization proper starts in the soap micelles, where the solubilized monomer becomes activated and where the polymer chain is propagated. After all the free soap has become adsorbed on the polymer particles, the latter are almost the sole loci of the further polymerization.

In order for a substance to act as an inhibitor or retarder in emulsion polymerization, it must be present at the locus where free radicals are formed, where they initiate polymerization, or where the polymer chains are growing. It is shown below that in this laboratory we have obtained good evidence that the activation of styrene by water-soluble catalysts occurs mainly in the "true" water phase and to a much lesser extent, if at all, in the soap micelles. The free radicals formed in the true aqueous layer must then be transferred to the soap micelle to initiate polymerization. If a substance which acts like an ideal inhibitor in bulk polymerization is water-soluble (e.g., oxygen, *p*-benzoquinone) it reacts in the "true" water phase with the free radicals formed there, and thus prevents the initiation of normal chain propagation. Such substances may react with radicals also at the soap micelle, and thus act like typical inhibitors even though their water solubility is low (e.g., chloranil).

A retarder is much less effective in its reaction with free radicals than is an inhibitor. If the retarder is water-soluble and insoluble in the monomer phase and in the micelles (e.g., nitrobenzoate in alkaline medium, nitrobenzenesulfonate, etc), it can react with some of the free radicals formed by the "catalyst" in the true aqueous layer, but it cannot interfere with the polymerization proper. It therefore exerts a retarding effect mainly by decreasing the rate at which free radicals reach the micelle, and hence the "effective" rate of activation. If the retarder is soluble in the monomer and in the micelles, it exerts the same retarding effect as in catalyzed bulk polymerization. Actually, experiments have substantiated this interpretation.

B. Experiments with retarders

It is shown in another paper (32) that 3,5-dinitrobenzoate in the emulsion polymerization of styrene with fatty acid soap as emulsifier and persulfate as "catalyst" acts like a mild retarder, its effect being very much less than that of an equimolar amount of *m*-dinitrobenzene. On the other hand, in acid medium (pH 1), with dodecylamine hydrochloride as emulsifier, practically all of the dinitrobenzoate is present in the form of the free acid in the organic phase and the soap micelles, only a negligible trace being present in the "true" aqueous phase. Therefore, at a pH of 1 3,5-dinitrobenzoate and *m*-dinitrobenzene are equally effective as retarders.

The mechanism of the retardation reaction has been discussed in the previous section under bulk polymerization. According to this mechanism, a retarder, which is present at the locus of the propagation reaction, should reduce the molecular weight of the polymer formed. This was found to be the case. An example is furnished by the effect of 0.052 and 6.64 millimoles of *m*-dinitrobenzene in the following recipe:

Styrene	100 g.
Water	185 g.
SF flakes	5.0 g.
Potassium persulfate	0.3 g.
Temperature	50°C.

The observed rates of conversion and intrinsic viscosities (in benzene at 30°C.) are:

m-DINITROBENZENE	RATE OF CONVERSION	η_i AT 30°C.
millimoles	*per cent/hour*	
0	65	13.8
0.052	27	9.1
6.64	0.77	0.95

If the retarder is not present at the locus of propagation, but is present in the true aqueous phase where activation occurs, the molecular weight of the polymer is hardly affected. This is illustrated by the effect of 2.65 millimoles of 3,5-dinitrobenzoic acid in the above recipe, with the addition of sodium hydroxide to a concentration of 0.03 *M*:

3,5-DINITROBENZOIC ACID	RATE	η_i AT 25°C.
millimoles	*per cent/hour*	
0	67	13.2
2.65	47	12.5

The effect of a retarder on the kinetics of the polymerization reaction can be derived on the basis of the mechanism given in Section II. Let M represent monomer, C catalyst, R· a monomer or polymer radical, r the retarder, and Rr· the stabilized radical formed by addition of retarder to a monomer or polymer radical:

$$\mathrm{M} + \mathrm{C} \rightarrow \mathrm{R}\cdot,\ \text{initiation:}^{3}\ \mathrm{dR}\cdot/\mathrm{d}t = K_1(\mathrm{M})(\mathrm{C}) \quad (1)$$

$$\mathrm{R}\cdot + \mathrm{M} \rightarrow \mathrm{R}\cdot,\ \text{propagation:}\ -\mathrm{dM}/\mathrm{d}t = K_2(\mathrm{M})(\mathrm{R}\cdot) \quad (2)$$

$$2\mathrm{R}\cdot \rightarrow \mathrm{R}_2,\ \text{normal termination:}\ -\mathrm{dR}\cdot/\mathrm{d}t = K_3(\mathrm{R}\cdot)^2 \quad (3)$$

$$\mathrm{R}\cdot + \mathrm{r} \rightarrow \mathrm{Rr}\cdot,\ \text{reaction with retarder:}\ -\mathrm{dR}\cdot/\mathrm{d}t = K_4(\mathrm{R}\cdot)(\mathrm{r}) \quad (4)$$

$$\mathrm{Rr}\cdot + \mathrm{R}\cdot \rightarrow \mathrm{Rr} + \mathrm{RH}\text{:}\ -\mathrm{dRr}\cdot/\mathrm{d}t = K_5(\mathrm{R}\cdot)(\mathrm{Rr}\cdot) \quad (5)$$

When the concentration of (r) is very large, we may assume as a first approximation that termination of growing polymer chains occurs largely by 4 and 5, and that 3 may be neglected. We then have at the steady state:

$$K_4(\mathrm{R}\cdot)(\mathrm{r}) + K_5(\mathrm{R}\cdot)(\mathrm{Rr}\cdot) = K_1(\mathrm{M})(\mathrm{C}) \quad (6)$$

$$-\frac{\mathrm{dM}}{\mathrm{d}t} = K_2(\mathrm{M})(\mathrm{R}\cdot) = \frac{K_1K_2(\mathrm{M})^2(\mathrm{C})}{K_4(\mathrm{r}) + K_5(\mathrm{Rr}\cdot)} \quad (7)$$

---

[3] It is quite possible that the initiation does not occur according to equation 1. The rate-determining step may be the rate of dissociation of the catalyst into free radicals, and the concentration of monomer will not then affect the rate of initiation.

Also, at the steady state the following relation holds:

$$K_4(\mathrm{R}\cdot)(\mathrm{r}) = K_5(\mathrm{R}\cdot)(\mathrm{Rr}\cdot), \text{ or} \tag{8}$$

$$K_4(\mathrm{r}) = K_5(\mathrm{Rr}\cdot) \tag{9}$$

Thus, instead of equation 6 we may write:

$$\frac{\mathrm{dM}}{\mathrm{d}t} = \frac{1}{2}\,\frac{K_1 K_2(\mathrm{M})^2(\mathrm{C})}{K_4(\mathrm{r})} \tag{10}$$

In the presence of a separate styrene phase we find (M) constant, or

$$-\frac{\mathrm{dM}}{\mathrm{d}t} = K\frac{(\mathrm{C})}{(\mathrm{r})} \tag{11}$$

It has been well established (33, 44) that in the normal emulsion polymerization of styrene without retarder and with persulfate as catalyst, the following relation holds:

$$-\frac{\mathrm{dM}}{\mathrm{d}t} = K(\mathrm{C})^n$$

where $n = 0.5$. This relationship has also been repeatedly observed for bulk and solution polymerization with oil-soluble catalysts. In the presence of 6.64 millimoles of *m*-dinitrobenzene in the above recipe, but using dodecylamine hydrochloride instead of SF flakes, n becomes 0.83. Thus, the predicted value of unity is approached but not reached even where the rate of polymerization is only about 1 per cent of the normal rate.

The predicted dependence of the rate of polymerization upon the reciprocal of the retarder concentration has been found to hold well at high concentrations of retarder.

Polarographic measurements of the rate of disappearance of *m*-dinitrobenzene (32) during the emulsion polymerization of styrene in the above recipe, but with dodecylamine hydrochloride as emulsifier, have shown that it disappears at about the same rate as *p*-benzoquinone (see Section III,C). Since *p*-benzoquinone probably does not copolymerize with styrene under the conditions of our experiments, it is evident that *m*-dinitrobenzene also does not copolymerize, and that the adduct radicals are entirely unreactive toward monomer, as we have postulated in the mechanism proposed earlier.

C. Experiments with inhibitors

For a study of the activation of a monomer in emulsion polymerization, it would be desirable to have available inhibitors which react with free radicals to produce finished molecules which do not affect the rate of polymerization after consumption of the inhibitor. The rate of consumption of such an inhibitor during the induction period would be equal to or would bear a simple ratio to the rate of activation of the monomer. Thus, the length of the induction period would be inversely proportional to the rate of activation. Unfortunately, benzoquinone and other quinones are not suitable inhibitors in emulsion polymerizations with fatty acid soaps, because the quinones are rapidly decomposed in the alkaline medium. However, we have found that in acid recipes at low pH (about 1), using cation detergents such as dodecylamine hydrochloride, *p*-benzoquinone behaves like an ideal inhibitor. These studies are still in progress, and the results will be reported at a later date. At this time, it may be stated that the induction periods caused by *p*-benzoquinone in the emulsion polymerization of styrene at pH 1, employing the recipe given above but with dodecylamine hydrochloride as emulsifier, are accurately proportional to the initial quantity of quinone (the curves resembling those of Foord (20; Fig. 1) for bulk polymerization), inversely proportional to the concentration of persulfate, and essentially independent of the concentration of emulsifier. The rate of disappearance of the quinone during the induction period is found to be 5.7×10^{-5} moles per hour per liter of aqueous phase at 50°C. in the above recipe, whereas at 90°C. in the bulk polymerization of styrene Foord found the rate of disappearance of quinone to be 2.2×10^{-4} moles per liter per hour. The rates of polymerization are 3.48 moles per liter per hour of aqueous phase for emulsion polymerization and only 0.117 mole per liter per hour for bulk polymerization. Since a much faster rate of polymerization is observed for emulsion polymerization in this recipe at 50°C. than for bulk polymerization at 90°C., although the rate of activation (as measured by the rate of quinone disappearance) is only about one-fourth as large, it appears that the rate of propagation and hence the molecular weight of the polymer must be very great in emulsion polymerization. This is actually the case. The intrinsic viscosities of the polymers formed during unretarded polymerizations (see Section III,B) probably correspond to molecular weights of at least 2–3 million.

In this laboratory, the induction period caused by oxygen in the emulsion polymerization of styrene according to the above standard recipe has been studied extensively, using fatty acid soap (SF flakes) as emulsifier and potassium persulfate as catalyst. It should be realized that qualitatively and quantitatively the effect of oxygen may vary with the type of catalyst (water- or oil-soluble, redox systems, etc.) used. Oxygen causes an induction period in the emulsion polymerization of styrene and of butadiene, and in the copolymerization of butadiene (75)–styrene (25). During the induction period the oxygen is consumed, and polymerization starts with its normal rate at the end of the induction period.

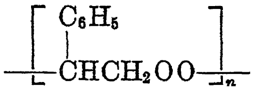
The reaction of styrene free radicals with oxygen is not so simple as their reaction with quinone. As we have mentioned in Section II of this paper, during the oxygen induction period in the emulsion polymerization of styrene with persulfate as catalyst (3), the free radicals formed in the activation reaction evidently react with oxygen with the formation of peroxide free radicals:

$$R\cdot + O_2 \rightarrow ROO\cdot$$

The peroxide free radicals then react very slowly (as compared to the reaction of monomer free radicals with oxygen or with monomer in the absence of oxygen) with monomer:

$$ROO\cdot + M \rightarrow ROOR\cdot$$

yielding a radical which then again rapidly reacts with oxygen, etc. A copolymer of styrene and oxygen is thus formed (polystyrene peroxide):



$$\left[\begin{array}{c} C_6H_5 \\ | \\ -CHCH_2OO- \end{array}\right]_n$$

This copolymer has actually been isolated and gave the following elementary analysis: calculated for $C_8H_8O_2$: C, 70.50; H, 5.86; O, 23.60. Found: C, 71.05, 71.13; H, 6.04, 6.17; O (by difference), 22.9, 22.6.

This substance released iodine from potassium iodide in acetic anhydride (although not quantitatively), catalyzed the bulk polymerization of styrene at 80°C., gave a characteristic reduction wave at the dropping-mercury electrode, and was found to decompose explosively at about 100°C. with formation of benzaldehyde and formaldehyde.

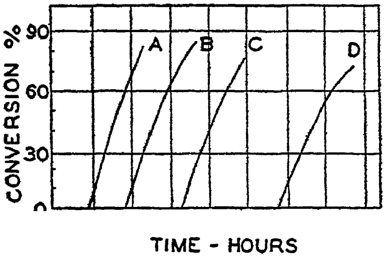


FIG. 3

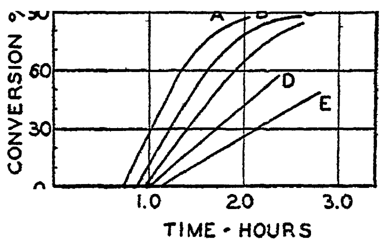


FIG. 4

FIG. 3. Induction periods produced by air in emulsion polymerization. Amounts of persulfate per 100 g. styrene: A, 0.6 g.; B, 0.3 g.; C, 0.15 g.; D, 0.075 g.

FIG. 4. Induction periods obtained using 0.6 part of persulfate and varying the concentration of the SF flakes emulsifier. SF flakes per 100 g. styrene: A, 5.0 g.; B, 2.5 g.; C, 1.25 g.; D, 0.625 g.; E, 0.313 g.

In the emulsion polymerization of styrene in bottles in the presence of oxygen, Kolthoff and Dale (34) have found:

(*1*) The induction period caused by oxygen in the emulsion polymerization of styrene with persulfate as "catalyst" is inversely proportional to the persulfate concentration, and proportional to the amount of oxygen provided the initial partial pressure of oxygen is constant, but not independent of the initial oxygen pressure when the initial volume is constant.

(*2*) The length of the induction period is hardly dependent upon the amount of soap in the charge, indicating that, as we have said earlier, the activation of the monomer occurs mainly in the "true" water phase and not in the soap micelles.

(*3*) Oxygen acts like a temporary shortstop when introduced into the mixture after the start of polymerization.

In figure 3 are represented the induction periods produced by 43 ml. of air in the polymerization of 210 ml. of emulsion made up according to the recipe on page 516, but employing varying amounts of persulfate, as indicated.

In figure 4 are represented the results obtained using 0.6 part of persulfate and varying the concentration of the SF flakes emulsifier.

The results shown in figures 3 and 4 closely resemble those found using quinone as inhibitor, except that much more oxygen than quinone is required to produce a given induction period. This more rapid rate of oxygen disappearance is a result of the chain reaction which it undergoes, and which quinone is capable of undergoing only to a much more limited extent if at all, under the conditions of our experiments.

Experiments by the present authors (3) have been carried out using a manometric apparatus by means of which the rate of oxygen consumption by the reaction mixture could be directly measured, and which allowed efficient mixing of the gas and liquid phases. It has been found that the rate of disappearance of the oxygen during the oxygen induction period in the emulsion polymerization of styrene is directly proportional to the persulfate concentration, but independent of the oxygen pressure. In the bottle experiments the induction period was not found to be independent of the initial oxygen pressure with a given volume of oxygen, apparently because under the conditions of agitation obtaining during bottle polymerizations, the oxygen does not attain solubility equilibrium.

These observations are consistent with a mechanism similar to that on page 513 but in which step 1 is an activation by persulfate rather than a thermal activation:

$$M + C \rightarrow R\cdot \qquad (1)$$

$$R\cdot + O_2 \rightarrow ROO\cdot \qquad (2)$$

as in 2a, 2b, 2c, etc. Since step 2 is much more rapid than step 1, step 1, which is independent of the oxygen pressure, becomes the rate-controlling step; hence the rate of consumption of oxygen is independent of its pressure.

Again, the rate of oxygen consumption is found to be nearly independent of the concentration of the SF flakes emulsifier employed.

After very long induction periods in the emulsion polymerization of styrene at 50°C., a slight increase in polymerization rate over that normally found may be observed. However, the peroxide polymer formed is too stable to have an appreciable effect unless present in considerable concentrations.

Bottle polymerizations according to the standard recipe with butadiene and with butadiene (75)–styrene (25) are now being carried out in this laboratory by J. M. Honig. Again, oxygen causes a typical induction period, the length of which is not inversely proportional to the persulfate concentration but to the square root of the persulfate concentration. As was found in the emulsion polymerization of styrene, the induction period caused by oxygen decreases only slightly with increasing concentrations of soap. Thus, again, the activation reaction appears to occur mainly in the "true" aqueous phase. These studies so far appear to indicate striking differences between the activation of styrene by persulfate on the one hand and of butadiene and butadiene (75)–styrene (25) on the other.

IV. PRACTICAL ASPECTS OF THE INHIBITION AND RETARDATION OF VINYL POLYMERIZATION

Inhibitors and retarders are of practical importance in the manufacture of synthetic rubber. In this section, we shall limit our brief discussion chiefly to the effects observed in the emulsion copolymerization of butadiene (75)–styrene (25), which is generally carried out with 100 parts of monomers, 180 parts of water, 5 parts of soap flakes as emulsifier, 0.3 part of potassium persulfate, and 0.5 part of dodecyl mercaptan. In this process, inhibitors and retarders are important for the following reasons:

(*1*) They are used to stabilize monomers against premature polymerization during synthesis, distillation, shipment, and storage. Such premature polymerization would lead to great loss both through waste of monomer and through fouling of equipment. Compounds falling in Foord's class of ideal or nearly ideal inhibitors may be expected in general to be the most effective stabilizers. Substances falling in the class of retarders will be effective stabilizers if present in sufficient quantity. Although not mentioned by Foord, we have seen that oxygen is a good inhibitor for the bulk polymerization of styrene, and probably for other monomers as well, provided the temperature is not too high.

(*2*) They may interfere with the normal rate of polymerization. Traces of inhibitors or retarders are added to commercial monomers as stabilizers. These stabilizers may interfere with the emulsion polymerization and must be removed by distillation or by other means if present in harmful concentrations. Phenolic substances can be removed by caustic washing.

In addition, retarding substances occur in technical butadiene and in technical soap flakes. These substances probably act in essentially the same manner as aromatic nitro compounds, i.e., they react very readily with monomer radicals to produce adduct radicals having a very much lower order of reactivity. The structure:

$$\text{—CH=CHCH}_2\text{CH=CH—}$$

which occurs in linoleic and linolenic acids (present in variable amounts in commercial soap flakes) and in 1,4-pentadiene (present in butadiene) has a particularly powerful retarding effect, although not so powerful as *m*-dinitrobenzene.

(*3*) They are employed to advantage to "shortstop" the polymerizing mixture when the desired conversion of monomer has been reached. Shortstops may function (*a*) by deactivating all or most of the free radicals produced in the system so that little or no normal chain propagation can occur, but without affecting the rate at which the radicals are produced, and (*b*) by destroying the "catalyst", and thus cutting off the supply of radicals at its source. Most shortstops used or proposed for use in commercial practice probably combine both actions, but action 1 is believed to be in general more important.

Hydroquinone, the most widely used shortstop, undoubtedly is first oxidized to *p*-benzoquinone, which is nearly an ideal inhibitor under suitable conditions. However, *p*-benzoquinone is not stable in alkaline medium but decomposes fairly rapidly to degradation products of unknown structure, and it is probably these degradation products which actually react with the free radicals.

Some indication of the practical importance of Foord's work (20) is furnished by the fact that his studies provide the basis for patents relating to the stabilization of styrene and to the accurate control of the period of stabilization. Styrene polymerized *in situ* is of importance in the electrical industry, and the bulk polymerization of vinyl monomers is of course of fundamental importance in the plastics industries. It can be readily seen that ideal inhibitors would be useful in handling these substances, since they allow polymerization to occur only after a definite and predictable interval.

Stabilization of monomers has become a problem of considerable industrial importance, since the manufacture of synthetic rubber has been put in operation on a large scale. Undesirable polymerization with the formation of resinous products has proved to be a great nuisance in the polymer-manufacturing plants and in the final stages of the manufacture of butadiene.

The growth of a resinous polymer of butadiene has recently been studied by Welch, Swaney, Gleason, and Beckwith (63). This polymer, which has been designated in the literature as "cauliflower" polymer but is now called "popcorn" polymer, is a tough, insoluble, infusible substance which forms in and frequently fouls the columns used for the distillation of butadiene. The growth of this substance is initiated by peroxides in the presence of rusty iron and moisture. Once growth has been initiated, polymerization proceeds rapidly on the surface of the polymer formed, provided monomer (vapor or liquid) is supplied, and the presence of catalyst is no longer required. Polymer growth can be retarded by mercaptobenzothiazole, *p*-quinone dioxime, and other vulcanizing agents and accelerators for vulcanization. Typical antioxidants are ineffective in retarding its growth.

The resinous copolymer of butadiene and styrene has been studied by Kharasch *et al.* (31b). This substance resembles the popcorn polymer of butadiene, but is somewhat more soluble in organic solvents. It forms where butadiene and styrene are present together at relatively high temperatures (75–100°C.), as in the monomer recovery units of the GR-S manufacturing plants, and also presents a serious fouling problem. It shows ability to grow in the presence of monomer from "seeds" of initially formed polymer. Its growth can be initiated by any substance having α-methylene groups capable of forming peroxides. Butadiene and its polymers, after exposure to oxygen, are such substances. Peroxidized and polymerized tung oil serves equally well. The activity of the seeds can be destroyed by nitrogen dioxide or nitrogen trioxide, which decomposes the peroxides necessary for the polymerization and combines with the double bonds present. The growth of polymer, even when active seeds are present, can be arrested by aqueous solutions of sodium nitrite. Aqueous sodium nitrite was also found to be an exceedingly effective inhibitor for the thermal polymerization of styrene (even at temperatures as high as 100°C.), provided the aqueous and oil phases were effectively agitated.

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REACTIONS IN THE SOLID STATE

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I. INTRODUCTION

The properties of solids may be divided into two groups: (*1*) structure-insensitive or coöperative properties, and (*2*) structure-sensitive properties (136). Structure-insensitive properties are well defined under given external conditions and are independent of the history of the specimen and of its dimensions. Structure-sensitive properties, on the other hand, are directly affected by factors like the mode of preparation of the specimen, the pretreatment, and the particle size and shape. To the structure-insensitive group of properties belong, among others, the chemical formula, the lattice dimensions, the true density, the specific heat, the thermal expansion, and for ideal lattices the electric conductivity and the absorption spectra. Examples of structure-sensitive properties are the mechanical strength and the actual value of the cohesion, and the electric conductivity and the absorption spectra (particularly the long-wave-length band) of real crystals.

The chemical reactivity, like several other properties, is structure-insensitive in only a few instances; usually it is structure-sensitive, as is exemplified most strikingly by the circumstance that the catalytic activity of a solid, or the ability to luminesce, may vary tremendously with different modes of preparation or treatment. In the subsequent discussion of reactions in the solid state considerable space is devoted to the few known structure-insensitive reactions since they, although of subordinate significance practically, provide a basis for a general understanding of structure-sensitive reactions.

Reactions in the solid state are defined as chemical processes in which one or more solid reaction products are formed with diffusion of elementary particles within their interior. The layer of reaction products increases by chemical reaction with the reactants adjacent to its boundaries. The reactants may be in any state of aggregation, but in this paper we are mainly concerned with reactions between solid reactants in which diffusion in the solid state is obviously required. Chemical changes of solids which do not involve penetration of particles through solid phases are, by definition, outside the scope of the present discussion. Furthermore, we omit reactions between metals, such as formation or decomposition of intermetallic phases and diffusion and transformation processes, since they are treated adequately in the metallographic literature. We restrict ourselves to reactions of inorganic solids which throughout will be considered as isotropic crystals. This simplification appears justified, since reactions between solids overwhelmingly occur with mixtures or between aggregates of fine powders. In principle, the considerations apply also to amorphous substances.

II. HISTORICAL NOTES

Despite their abundance, reactions in the solid state have remained unrecognized for a long time. After some familiarity had been gained on solid-phase diffusion in metals—the first observation of this kind seems to be due to Faraday (27) in 1820—Spring claimed in 1885 (137) to have observed reactions between inorganic solids; but his interpretation of the observations was partly erratic. In 1910 Cobb (15) described reactions between quartz and alumina with calcium carbonate or calcium sulfate, typical reactions in the solid state which, however, were not recognized clearly by him. Since 1912 it has been pointed out by Hedvall (43, 44, 45, 46) that reactions in the solid state occur frequently and represent indeed an important branch of chemistry. In the past thirty years intensive investigations have been carried out in this field, as evidenced by the monographs of Hedvall (52) and Jost (99).

III. THERMODYNAMIC RELATIONS

Except for cases of miscibility of reactants and product phases, equilibrium is usually not possible in reactions in the solid state and reactions proceed exothermically until at least one of the reactants is completely consumed. In practice, of course, complete reaction is difficult to achieve; it is essential that mixtures of fine powders be pulverized repeatedly to remove the barrier of product layers between the reactants. The equilibrium conditions have been discussed in detail by Tammann (142). For the attainment of a state of equilibrium either liquid or gaseous phases must partake in the reaction, or the heat of reaction must be small, and the difference of entropies of reactants and products must not be zero. In the last case, equilibrium occurs at a single temperature,[1] where the stability of the system is reversed. Below the equilibrium temperature the products are formed, and above the equilibrium temperature they are decomposed into the reactants, the reaction always proceeding exothermically.

The number of phases which may be formed in mutually soluble solids is determined by the constitution diagram. However, since concentration gradients are prerequisites for the occurrence of diffusion, only phases having two or more degrees of freedom can be formed at ordinary pressures, while phases with one degree of freedom appear as interfaces between the layers of products (125). Thus, in a binary system only one-phase layers are possible as reaction products. The thermodynamic requirements are, however, by no means a safe criterion for determining which phases actually will be formed in a reacting system. Since the particle motion in solids is strongly resisted and requires large energies of activation, unstable phases might form and coexist with other phases for practically unlimited times, if the temperature is sufficiently low. Even when the reaction products are the thermodynamically required phases, they may appear in thermodynamically unstable states characterized by an excess energy content. These states are designated as active phases, and their rôle in the reactivity of solids cannot be overemphasized. These are discussed more fully in a later section.

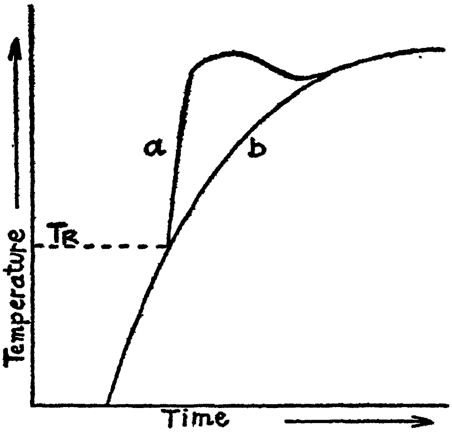

FIG. 1. Observation of solid-state reactions by means of heating curves (Hedvall (47))

Systems composed exclusively of solids are exothermic, and in order to investigate these reactions isothermically, the rate has to be kept at an appropriate low value, for instance, simply by pressing the reactants against each other in the form of pellets instead of using powder mixtures. On the other hand, the fact that powder mixtures can be readily heated up, owing to the low specific heats and low heat conductivities of crystals, may be utilized in the study of the reactions by means of heating curves (47), as illustrated in figure 1. Upon heating the powder mixture, reaction begins to proceed with great intensity at a certain temperature (T_R). Thereafter, the temperature of the mixture (curve a) is considerably higher than the temperature obtained with the same mixture after reaction has ceased to occur (curve b). The "reaction temperature," although not sharply defined, is useful for characterizing a reaction system. From the area enclosed between curve a and curve b and from the analytically determined yield of the reaction, the heat of the reaction can be approximately calculated (142). In cases in which the heat of reaction is large, the reaction may sometimes proceed almost explosively as the "reaction temperature" is reached. Owing to the rise in temperature after reaction has begun to occur, liquid phases may be formed. It is, therefore, necessary to ascertain whether a reaction proceeds throughout as solid-phase reaction or in the later stages with liquid phases as vehicle.

---

[1] At high pressures equilibrium might exist at all temperatures if the molar volume of the products is larger than the sum of the molar volumes of the reactants. Such cases are of little practical significance.

IV. TYPES OF REACTIONS

Independent of the number of reactants, the reactions in the solid state can be considered as being composed of reactions between two components only, because chemical combination is possible only at the phase boundary between adjacent phases. An illustration of such subdivision is the formation of the ternary compounds $2CaO \cdot Al_2O_3 \cdot SiO_2$ and $CaO \cdot Al_2O_3 \cdot 2SiO_2$ from quartz, alumina, and calcium oxide, where it was found (95) that two of the three components combine as a first step, and then the third component reacts with this combination as a second step. Therefore, in classifying reactions in the solid state only reactions between two components need be considered.

Frequently, instead of the reactants directly, one uses compounds which decompose at the temperatures of the reaction into the desired reactants and into gaseous products: for instance, reactions between oxides may be attained by heating mixtures of carbonates, nitrates, sulfates, etc. Any accompanying gas development does not basically alter the nature of the solid-phase reaction. Such compounds are preferably used when the reactants proper are of low stability (for example, barium carbonate instead of barium oxide), or when the enhanced reactivity of freshly formed solids is of advantage, as is described in a subsequent section.

A. Additive reactions

The simplest and most frequently occurring type is the additive reaction $A + B \rightarrow AB$, where A and B may be elements or compounds. If the product (AB), through which the reaction has to proceed by diffusion, is not miscible with A and B, it is formed as a separate new phase between A and B. If AB is entirely or partly miscible with A or B, it is generated as one or two new phases within the original phases. It is also possible that A and B form consecutively products of different composition so that several phases may be present between the reactants.

Reactions between elements: An example of reactions between elements is that of the tarnishing of metals, in which a salt (oxide, halide, sulfide, etc.) is formed by reaction with a non-metal. A coherent diffusion layer may be formed in all instances in which the equivalent volume of the salt is greater than that of the metal (118). A few tarnishing reactions are structure-insensitive and are outstanding illustrations of the fundamental mechanism of reactions of solids. Mostly, however, such reactions are complex processes, as indicated by the examples listed in table 1, for which no adequate theory has as yet been developed.

Reactions between elements and compounds: These reactions constitute a comparatively small group of combinations like the following (10):

$$Mn + Mn_3O_4 \rightarrow 4MnO;\ Fe + 2FePO_4 \rightarrow Fe_3(PO_4)_2$$

Reactions between compounds: Compounds which combine additively are mostly binary; there are however exceptions, for example, the formation of magnesium orthosilicate from the metasilicate and magnesium oxide (39, 96) may be mentioned.

TABLE 1

Examples of tarnishing reactions

REACTING COMPONENTS	REACTION PRODUCTS IDENTIFIED IN TARNISH LAYER	REFERENCES
Al + air (or O_2)	Amorphous, ϵ-, β-, γ-Al_2O_3	(12, 140)
Cu + air (or O_2)	Cu_2O, CuO	(74)
Fe + air (or O_2)	Fe–O*, FeO, Fe_3O_4, Fe–Fe_2O_3,* α-, γ-Fe_2O_3	(6, 29, 117, 154)
Cu–Zn* + O_2	Cu_2O, ZnO	(20)
Cr–Ni* + air	Cr_2NiO_4	(79)

* – designates solid solution.

There have been prepared solid solutions of systems exhibiting either complete miscibility, like CoO–ZnO (44), CoO–MgO (44, 73), CoO–MnO (45), CoO–NiO (45, 73), NiO–MnO (48), NiO–MgO (48, 73), CaO–CdO (114), BaO–SrO (14, 24), Fe_2O_3–Cr_2O_3 (116, 166), or exhibiting partial miscibility, like Al_2O_3–Cr_2O_3, Al_2O_3–Fe_2O_3 (116), Fe_2O_3–Mn_2O_3 (166), CdO–MnO, MgO–MnO (115).

Compounds are formed either by combination of salts to yield double salts, such as Ag_2HgI_4 from silver iodide and mercuric iodide (103), Ag_4PbI_6 from silver iodide and lead iodide (152), or by combination of an acidic reactant with a reactant of basic nature to yield a salt. Reactions of the acid oxides SiO_2, TiO_2, ZrO_2, WO_3, MoO_3, V_2O_5, Sb_2O_3, As_2O_3 with the basic oxides BaO, BeO, CaO, CdO, CuO, FeO, MgO, NiO, PbO, SrO, ZnO have been early reported (142). The formation of stannates (45), uranates (145), columbates, and tantalates (92) was likewise described at an early stage. In more recent years particularly, chemical reactions of oxides have been explored systematically, i.e., reactions involving the formation of compounds like silicates, aluminates, spinels, titanates, ferrites, chromites, etc. For a survey of this field, reference is made to the monograph by Hedvall (52). The compounds formed may exhibit appreciable miscibility with one or both of the reactants (13, 17, 71, 105).

A special group of unusually intensive reactions comprises reactions involving a peroxide as a reactant which decomposes in the course of the reaction at temperatures at which the peroxide itself ordinarily is stable. As a result of the decomposition of the peroxide, other substances or the reaction products may be oxidized. In reactions between BaO_2 and Cr_2O_3, U_3O_8, MnO, or Fe_2O_3, the chromate, uranate, manganate, and ferrate are rapidly formed (49, 61, 67). In other cases, a substance may become oxidized without combination with the peroxide, for instance, Cu_2O by BaO_2 at 260°C. (61), or the reaction with the peroxide may be accelerated by the decomposition, even when no oxidation is possible, for instance, $BaO_2 + SiO_2$ or TiO_2 (67), $CeO_2 + SiO_2$, WO_3, or V_2O_5 (142). Reaction between BaO_2 and SiO_2 sets in at 300°C. These reactions occur in the solid state, since BaO_2 dissociates at 795°C. and liquid phases, owing to the presence of traces of $Ba(OH)_2$ in BaO_2, do not exist below 390°C.

No general rules have been found for additively reacting systems except that the reaction temperatures often approximately coincide with the temperatures at which self-diffusion becomes appreciable within one of the reactants (142). A relation of the temperatures of measurable self-diffusion to the absolute melting temperatures was first proposed by Tammann and Mansuri (144). The ratio between the two temperatures is approximately 0.3 for metals, 0.5 for inorganic substances, and 0.9 for organic compounds.

B. *Exchange reactions*

The second mode of reaction between two solids is by exchange of constituents according to one of the following schemes:

$$A + BC \rightarrow AC + B \tag{a}$$

$$AB + CD \rightarrow AD + BC \tag{b}$$

$$ABX + CB \rightarrow CBX + AB \tag{c}$$

In these reactions, which involve diffusion through two product layers, it is possible to have a considerable variety of phase arrangements, determined by the miscibilities of product and reactant phases and by the reaction mechanism (nature of mobile particles and their relative velocities). The way in which the products may be arranged between the reactants is either beside each other or tandem. An illustration of the possibilities is the following simple case: in the reaction $AB + CD \rightarrow BC + AD$, the product AD may be miscible with AB, while all other phases are not miscible. If the reaction is carried out by a migration of B and D only, B diffusing from AB through the product layer towards CD and D diffusing from CD towards AB, the succession of layers (B, D)A | BC | CD may occur. If, on the other hand, A and C are the mobile particles in the reaction, the layers might be AB | BC | AD | CD, without formation of a solid solution of AB and AD. In equivalent mixtures the reactants should, of course, ultimately be completely consumed. The conditions of phase formation are still more complicated when ternary or higher compounds react, and when products of different nature are formed during the course of a reaction.

Examples of reactions according to scheme (a) are found in the exchange of the metal of a salt for a more electropositive one such as: $Cu + HgCl_2 \rightarrow CuCl + HgCl$; $Fe + CuO \rightarrow FeO + Cu$; $Fe + PbSO_4 \rightarrow FeSO_4 + Pb$; $Mg + ZnS \rightarrow MgS + Zn$ (142); $Mg + CdO \rightarrow MgO + Cd$; $2Al + 3NiO \rightarrow Al_2O_3 + 3Ni$; $Zn + CuO \rightarrow ZnO + Cu$; $Sn + CuO \rightarrow SnO + Cu$ (37); $Cu + AgCl \rightarrow CuCl + Ag$; $Co + Cu_2O \rightarrow CoO + 2Cu$ (162). In such systems reactions have been observed to be rapid when the heat of reaction is large.

Reactions conforming to scheme (b) are exemplified by the following: $CuI + Ag_2S \rightleftarrows (Cu, Ag)_2S + (Cu, Ag)I$; $Cu_2Se + Ag_2S \rightleftarrows (Cu, Ag)_2S + (Cu, Ag)_2Se$ (152); $BaO + 2CuI \rightarrow BaI_2 + Cu_2O$; $BaO + PbCl_2 \rightarrow BaCl_2 + PbO$; $BaO + NiBr_2 \rightarrow BaBr_2 + NiO$; $BaO + 2TlBr \rightarrow BaBr_2 + Tl_2O$; $CaO + NiCl_2 \rightarrow CaCl_2 + NiO$; $CaO + PbCl_2 \rightarrow CaCl_2 + PbO$ (57); $PbS + CdSO_4 \rightarrow PbSO_4 + CdS$; $HgCl_2 + 2KI \rightarrow HgI_2 + 2KCl$; $PbCl_2 + 2KI \rightarrow PbI_2 + 2KCl$ (102). For each system in this group individual reaction temperatures were found. These temperatures are, in corresponding cases, lower for barium oxide than for calcium oxide, indicating that the basic strength of the reactant influences the reaction temperature. On the other hand, the observed temperatures in the reactions between barium oxide and cupric halides (51) coincided with the temperatures at which self-diffusion becomes appreciable in the halide (153).

Exchange reactions between alkali halides have been investigated extensively (107). In all instances in which the lack of miscibility precluded establishment of equilibrium, large cations combined with large anions, and small cations with small anions—for instance, sodium bromide and potassium chloride react to form sodium chloride and potassium bromide—whereas no reverse reaction takes place. This is a direct result of the requirement that reactions in systems without miscibility have to proceed exothermically. Thus with alkali halides the direction of reaction can be derived from the difference in lattice energy of the compounds involved.

Reactions according to scheme (b) may also occur in combination with other reactions. For instance, an easily oxidizable sulfide may react with a basic oxide with formation of free metal in the following way:

$$4MeO + 4Me'S \rightarrow 4Me'O + 4MeS$$

$$4Me'O + MeS \rightarrow 4Me' + MeSO_4$$

These reactions take place between barium oxide and sulfides of copper or lead (8).

In the presence of oxygen the products of exchange reactions may become oxidized. Thus, reactions of sulfides, phosphides, carbides, and silicides with basic oxides yield directly sulfates, phosphates, carbonates, and silicates of the basic oxide in question (63). Frequently these reactions proceed at relatively low temperatures and may be used to prepare compounds of low thermal stability. It should be noted that nitrates are not obtainable from nitrides in this way. The reaction temperatures of these systems vary individually, but under comparable conditions are lower, the more basic the oxide.

Reactions according to scheme (c) comprise a large group of reactions in which an oxygen-containing acid group is exchanged between one basic oxide and another: $MeO + Me'XO_n \rightarrow Me'O + MeXO_n$. Reactions of this type, explored by Hedvall (60), are listed in table 2. The reaction temperatures in this group again show the correlation with the basic nature of the oxide involved; moreover, in contrast to the other types described, these reactions have in common the fact that the reaction temperatures for a given basic oxide are approximately constant and independent of the nature of the other reactant (carbonate, sulfate, phosphate, or silicate). The same is also approximately true in corresponding reactions between CaO, SrO, BaO and spinels like $ZnAl_2O_4$, $CoAl_2O_4$, $CoCr_2O_4$, $FeCr_2O_4$, $CuAl_2O_4$ (50). Some reactions, which at first glance appear to proceed as additive reactions, are actually exchange reactions of the same type; for example, the formation of cobaltite from Co_3O_4 and ZnO (62), or of ferrites from Fe_3O_4 and MgO, CoO, NiO, MnO (7) takes place in the following way:

$$ZnO + CoOCo_2O_3 \rightarrow ZnOCo_2O_3 + CoO, \text{ etc.}$$

A satisfactory explanation for the exceptionally constant reaction temperatures in this last group for a given oxide cannot yet be given (52, 56), but this regularity appears to hold rigorously and is only suspended—for reasons discussed in a later section—when the acidic reactant undergoes crystallographic transition below the temperature at which it normally would react with the basic oxide.

V. FORMAL REACTION KINETICS

The over-all reaction rates are determined by the following factors:

1. The spatial and temporal sequence in which all possible phases appear.
2. Phase boundary processes, which may include
   (a) transfer of matter from one phase to the other,
   (b) chemical reactions,
   (c) formation of nuclei and growth of the reaction products.
3. Diffusion in the layer of reaction products.

In order to ascertain the rate-determining conditions it is useful to trace the chemical potential of the diffusing particles in the different phases. A simple example is given in figure 2, which shows an additive reaction between two solid components (A, B) yielding only one definite product (AB) immiscible in A or B. When only the component A is able to move, two different cases are possible:

(*a*) The phase boundary processes are so rapid that equilibrium is continuously established at the boundaries during the entire course of the reaction. Under these conditions the diffusion in the product layer alone is rate-determining.

(*b*) The phase boundary processes are not infinitely rapid compared with the diffusion velocity. Since both the transition of A particles from phase A to phase AB at phase boundary I and the formation of fresh AB at phase boundary II require time, equilibrium is not established at the phase boundaries. The diffusing substance is accumulated at phase boundary II. Under conditions otherwise equal, the gradient of the chemical potential is smaller than in case

TABLE 2

Reaction temperatures of exchange reactions between alkaline earth oxides and salts of oxygen-containing acids

SALT COMPONENT	REACTION TEMPERATURE WITH BaO	REACTION PRODUCTS	REACTION TEMPERATURE WITH SrO	REACTION PRODUCTS	REACTION TEMPERATURE WITH CaO	REACTION PRODUCTS
	°C.		*°C.*		*°C.*	
Carbonates:						
$SrCO_3$	395	$BaCO_3 + SrO$				
$CaCO_3$	345	$BaCO_3 + CaO$	465	$SrCO_3 + CaO$		
$MgCO_3$	345	$BaCO_3 + MgO$	455	$SrCO_3 + MgO$	525	$CaCO_3 + MgO$
Sulfates:						
$SrSO_4$	370	$BaSO_4 + SrO$				
$CaSO_4$	370	$BaSO_4 + CaO$	450	$SrSO_4 + CaO$		
$MgSO_4$	370	$BaSO_4 + MgO$	440	$SrSO_4 + MgO$	540	$CaSO_4 + MgO$
$ZnSO_4$	340	$BaSO_4 + ZnO$	425	$SrSO_4 + ZnO$	520	$CaSO_4 + ZnO$
$CuSO_4$	345	$BaSO_4 + CuO$	420	$SrSO_4 + CuO$	515	$CaSO_4 + CuO$
Phosphates:						
$Sr_3(PO_4)_2$	350	$Ba_3(PO_4)_2 + SrO$				
$Ca_3(PO_4)_2$	340	$Ba_3(PO_4)_2 + CaO$	450	$Sr_3(PO_4)_2 + CaO$		
$Pb_3(PO_4)_2$	335	$Ba_3(PO_4)_2 + PbO$	455	$Sr_3(PO_4)_2 + PbO$	525	$Ca_3(PO_4)_2 + PbO$
$Co_3(PO_4)_2$	355	$Ba_3(PO_4)_2 + CoO$	465	$Sr_3(PO_4)_2 + CoO$	520	$Ca_3(PO_4)_2 + CoO$
$CrPO_4$	340	$Ba_3(PO_4)_2 + Cr_2O_3$	465	$Sr_3(PO_4)_2 + Cr_2O_3$	515	$Ca_3(PO_4)_2 + Cr_2O_3$
$Ag_4P_2O_7$	330	$Ba_3(PO_4)_2 + Ag_2O$*	450	$Sr_3(PO_4)_2 + Ag_2O$*	510	$Ca_3(PO_4)_2 + Ag_2O$*
Silicates:						
$CaSiO_3$ (wollastonite)	355	Barium silicate + CaO	455	Strontium silicate + CaO		
$MgSiO_3$ (enstatite)	355	Barium silicate + MgO	455	Strontium silicate + MgO	560	Calcium silicate + MgO
$MnSiO_3$ (rhodonite)	355	Barium silicate + MnO	465	Strontium silicate + MnO	565	Calcium silicate + MnO
Al_2SiO_5 (sillimanite)	355	Barium silicate + Al_2O_3	430	Strontium silicate + Al_2O_3	530	Calcium silicate + Al_2O_3

(a), and the reaction is slowed down. With increasing width of the layer of AB, the influence of diffusion on the rate increases, so that finally case (b) might change into case (a).

Case (a) is simpler than case (b) because there all phase boundary processes can be neglected. On the other hand, in the primary stages of the reaction, where the diffusion layers are extremely thin, or where there is very rapid diffusion, the phase boundary processes may become predominant and may be studied undisturbed by diffusion effects.

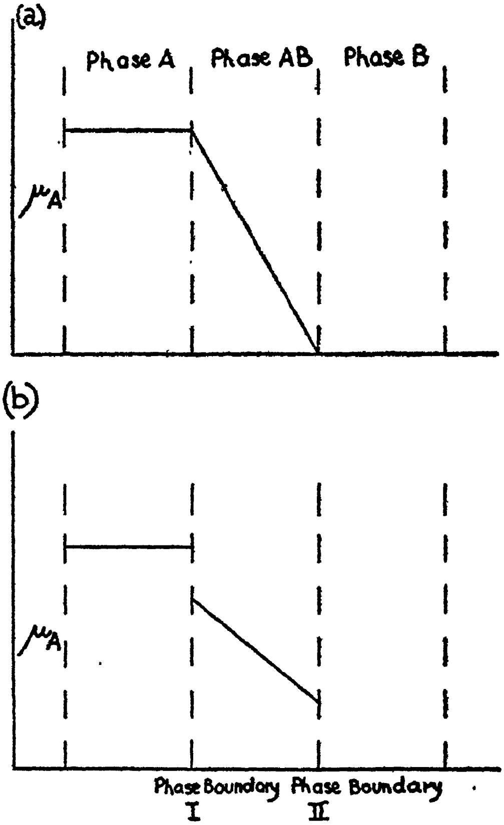

FIG. 2. Gradient of chemical potential of diffusing reactant

The conditions outlined can be expressed in a general way. Introducing a "reaction resistance" (W_R) for the phase boundary processes defined as the reciprocal of the velocity of all phase boundary processes, and introducing a corresponding "diffusion resistance" (W_D) for the diffusion processes in the product layer (28), the reaction rate may be written:

$$\frac{dn}{dt} = C \frac{\Delta\mu}{W_R + W_D} \tag{1}$$

where $\Delta\mu$ represents the free-energy change involved in the reaction. If we have case (a) of figure 1, $W_D \gg W_R$. The rate is diffusion controlled and equation 1 is transformed into:

$$\frac{dn}{dt} = C\frac{\Delta\mu}{W_D} = C\frac{\Delta\mu}{\frac{1}{D}\int_{\text{Phase boundary II}}^{\text{Phase boundary I}} d\xi/A} \tag{1a}$$

where D = diffusion coefficient as defined by Fick's law (4, 99),
ξ = thickness of diffusion layer, and
A = cross-sectional area of diffusion layer.

If the diffusion layer has a constant cross section, and if furthermore D also has a constant value, the reaction rate becomes:

$$\frac{dn}{dt} = \frac{A}{\xi}CD\Delta\mu = \frac{A}{\xi}k \tag{1b}$$

Expressing finally the reaction rate in terms of the growth of the product layer, the rate is:

$$\frac{d\xi}{dt} = \frac{k'}{\xi}; \qquad \xi^2 = k't \tag{1c}$$

This equation has been frequently verified, notably in a number of tarnishing reactions (21) and in additive reactions between solids, for example, in the following systems:

$BaCO_3 + SiO_2$ (85)
$BaCO_3 + MoO_3$ (85)
$Na_2CO_3 + SiO_2$ (38)
Na_2CO_3 or $CaCO_3 + SiO_2$, $3Al_2O_3 \cdot 2SiO_2$ (mullite), Al_2O_3 (120)
$BaCO_3 + Fe_2O_3$ (165)
$PbO + PbSiO_3$, Pb_2SiO_4 (82)

When—as is frequently the case—the reacting systems consist of mixtures of fine powders containing one of the reactants in large excess, the measurements may be evaluated by a relation proposed by Jander (85)

$$(1 - \sqrt[3]{1-\alpha})^2 = \frac{C}{R^2}t = C''t \tag{2}$$

where α = fraction of completion of reaction, and R = grain radius of the minor component assumed to be monodisperse and completely surrounded by the excess reactant. This equation appears to be applicable to many experimental results, although based on the assumption of a linear concentration gradient and a constant diffusion cross section which is not true for spherical particles. Serin and Ellickson (132) demonstrated that equation 2 for spherical particles is not nearly as good an approximation to the exact solution based on Fick's law as is equation 1c for the linear case. These authors recalculated Jander's (85) experimental data, using the exact equation:

$$1 - \alpha = \frac{6}{\pi^2} \sum_{n \text{ odd}} \frac{1}{n^2} \exp\left(-n^2 \pi^2 Dt/R^2\right) \tag{2a}$$

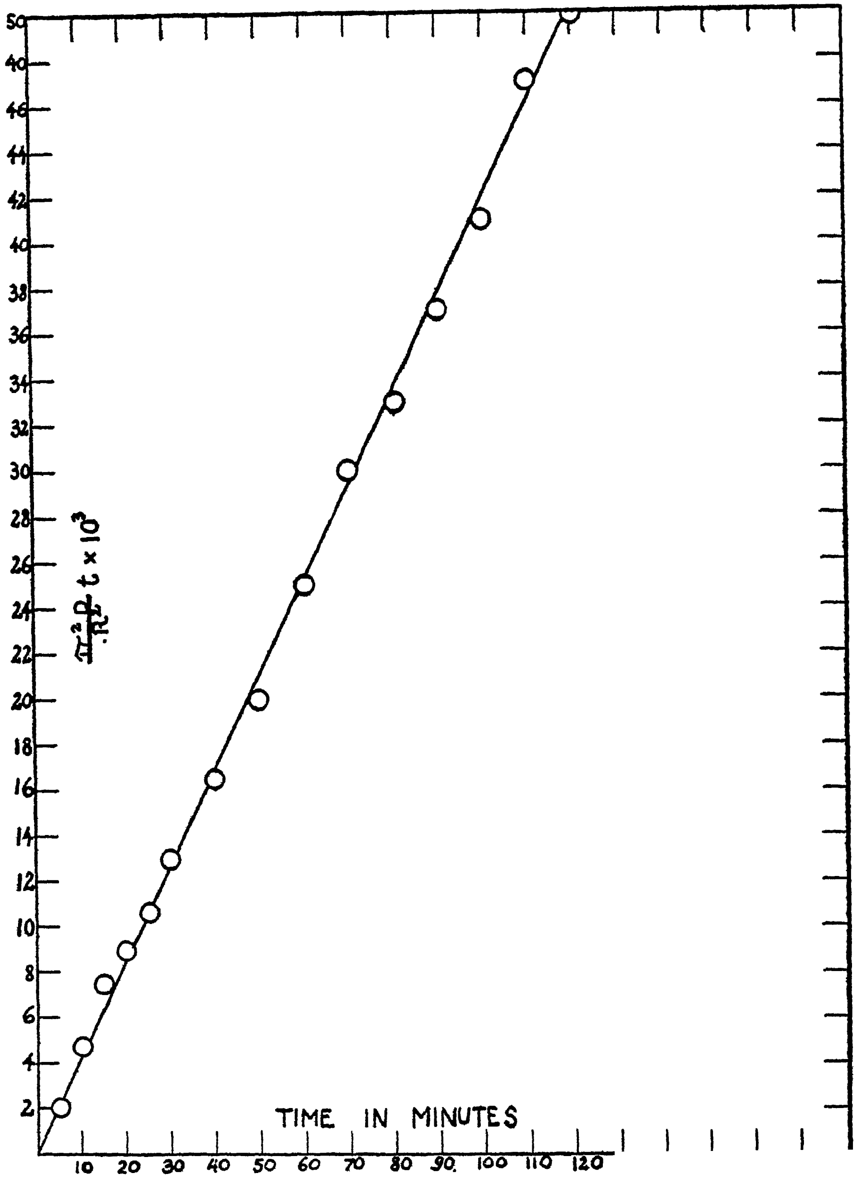

FIG. 3. Reaction rate of system $BaCO_3 + SiO_2$ (Serin and Ellickson (132))

In figure 3 are given the results for the reaction between barium carbonate and silicon dioxide at 830°C.; and figure 4 shows that the dependence of the rate on

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[2] This equation was previously given by Dünwald and Wagner (19) but not applied to reactions between solids.

the grain radius of barium carbonate, the minor constituent in these measurements, was in agreement with the theoretical requirements.

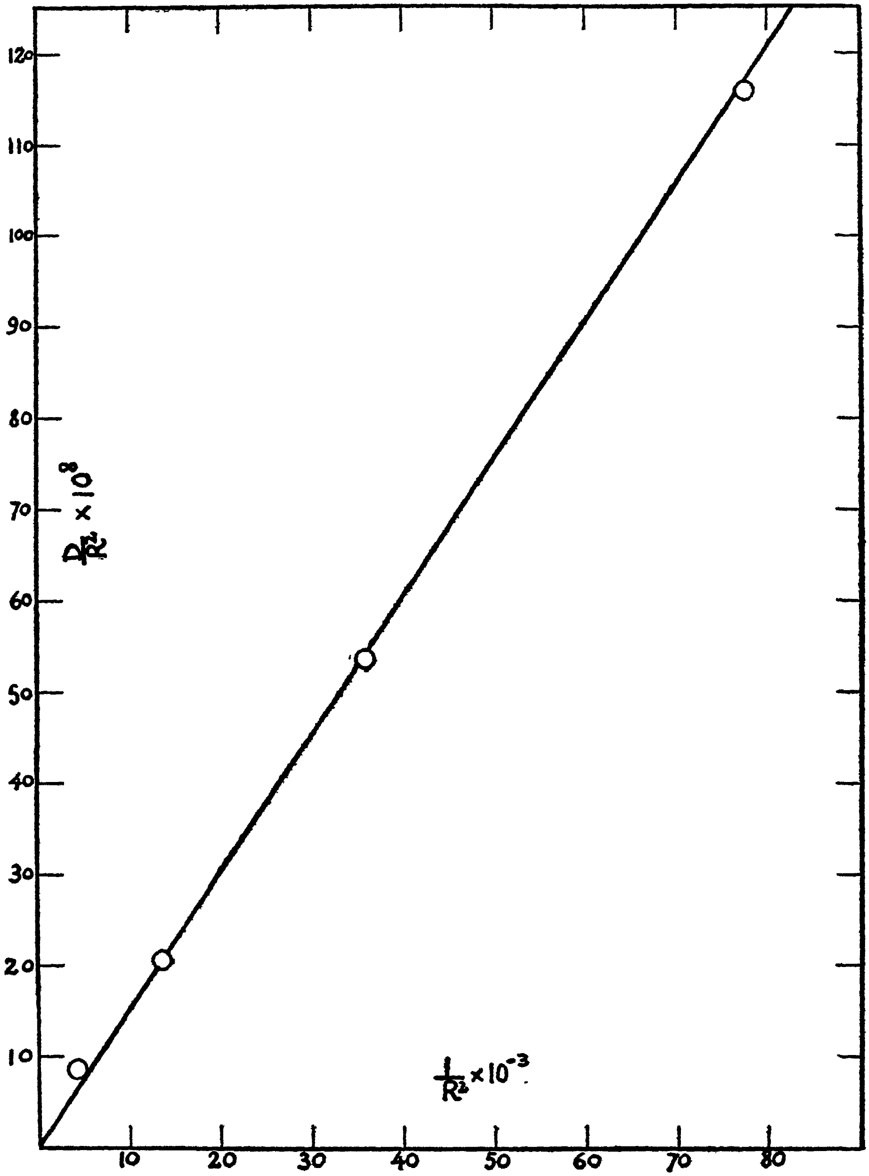

Fig. 4. Dependence of reaction rate in system $BaCO_3 + SiO_2$ on grain diameter of $BaCO_3$ (Serin and Ellickson (132)).

When the phase boundary processes cannot be neglected (case (b), figure 2) $\Delta\mu$ may be divided into two parts, $\Delta\mu'$ and $\Delta\mu''$, representing the changes of chemical potential due to the phase boundary processes and to the diffusion, respectively. Since, with increasing thickness of the diffusion layer, the influence of the phase boundary processes diminishes until it eventually vanishes, in a first approximation $\Delta\mu'$ may be assumed to be proportional to $1/\xi$ in the form (99):

$$\Delta\mu' = \Delta\mu \frac{b}{\xi + b}$$

(i.e., for $\xi = 0$: $\Delta\mu' = \Delta\mu$, and for $\xi \rightarrow \infty$: $\Delta\mu' = 0$). Thus the gradient of the chemical potential across the diffusion layer becomes:

$$\Delta\mu'' = \Delta\mu - \Delta\mu' = \Delta\mu \frac{\xi}{\xi + b}$$

which, introduced in rate expression 1b, yields:

$$\frac{\mathrm{d}n}{\mathrm{d}t} = CD\Delta\mu \frac{A}{\xi + b}$$

or transformed for integration:

$$\frac{\mathrm{d}\xi}{\mathrm{d}t} = \frac{k'}{\xi + b}; \qquad \xi b + \xi^2 = kt \tag{1d}$$

In the first stages of the reaction where the diffusion layer is thin, equation 1d reduces to linear growth: $\xi \sim k''t$. Subsequently, the rate should obey the complete expression 1d; thereafter, when the diffusion layer has become sufficiently thick, the square law of equation 1c should apply. Indeed, equation 1d has been confirmed in the oxidation of iron by carbon dioxide (112) and by water vapor (29).

For small values of ξ, equation 1d can be transformed (99) into:

$$b^2(e^{\xi/b} - 1) \sim k''t \tag{1e}$$

which likewise has been confirmed in some tarnishing reactions (143), although in a stage where the square law would be expected actually to hold. Similar empirical equations of the form:

$$\frac{1}{t} = \frac{1}{\alpha_1 e^{b_1\xi}} + \frac{1}{\alpha_2 e^{b_2\xi}} \tag{1f}$$

have been reported to represent the oxidation of copper, iron, zinc, and aluminum under certain conditions (108).

In the other extreme, where $W_R \gg W_D$, the rate is controlled solely by the phase boundary reactions. Owing to the complex nature of phase boundary processes, general rate expressions cannot be formulated but have to be established individually in each particular case. Under special conditions some reactions have been observed to proceed with constant speed (reduced form of equation 1d), such as:

$MgO + Ag_2SO_4 \rightarrow MgSO_4 + Ag_2O$ (respectively, $2Ag + \frac{1}{2}O_2$) (83)

$3MgO + 2Ag_3PO_4 \rightarrow Mg_3(PO_4)_2 + 3Ag_2O$ (respectively, $6Ag + 1.5O_2$) (83)

$MgO + Mg_2P_2O_7 \rightarrow Mg_3(PO_4)_2$ (84)

Sometimes, solid materials can be investigated only in powder form. Since reactions between solids are exothermic in the absence of reacting gases or liquids, and since the heat conductivities of non-metallic solids are usually low, the powder mixtures become heated during reaction, and kinetic derivations holding for isothermic systems cannot be used. A method to evaluate approximately kinetic measurements of non-isothermic systems is due to Jander (86). The temperature coefficient of the reaction rate may be expressed empirically as an exponential function: $k = C \exp(-Q/RT)$. When the reaction is initiated at a given temperature (T_e), the temperature of the reaction mixture rises almost instantaneously to the maximum temperature (T_i), from which it gradually decreases to the external temperature (T_e) as the reaction progresses. In the beginning we have thus $k_i = C \exp(-Q/RT_i)$, and at any time thereafter $k = C \exp(-Q/RT)$, where $T > T_e$. This yields:

$$k = k_i \exp\left(-\frac{Q}{R}\frac{T_i - T}{T_i \times T}\right) \tag{3}$$

Assuming that $T_i - T$ is proportional to the thickness of the product layer formed, and since $T_i \times T$ is approximately constant, we obtain $k = k_i \exp(-c\xi)$, which, introduced into equation 1c, yields:

$$\xi^2 = 2k_i t \exp(-c\xi) \tag{1g}$$

This equation was found (86) to describe adequately the observed rates of the reactions:

$$BaCO_3 + WO_3 = BaWO_4 + CO_2 + 10 \text{ kg.-cal.}$$

$$Ag_2SO_4 + PbO = PbSO_4 + Ag_2O \text{ (resp., } 2Ag + \tfrac{1}{2}O_2) + 3 \text{ kg.-cal.}$$

The rate constants determined by these or other equations are more or less structure-sensitive and cannot be employed directly to establish a reaction mechanism. Occasionally this might be due to a concentration dependence of the diffusion coefficients. Two reasons, however, appear to be mainly responsible for this state of affairs. The first is the complexity and irreproducibility of the phase boundary processes. The state of solid surfaces and the degree of contact between them are ill-defined and scarcely reproducible, especially in reactions in the solid state where the boundaries of the reaction layer expand continuously. While the kinetic treatment of nucleation and growth in the change from one phase to a new one offers considerable difficulties (155), the practically more important case of heterogeneous systems involving solids can hardly be treated theoretically at the present. Thus, despite their great significance in reactions of solids, phase boundary processes can seldom be brought under controlled conditions. It is, therefore, advisable to choose—if feasible—for kinetic investigations conditions such that equilibrium is continuously maintained at the phase boundaries; that is, that the phase boundary processes do not influence the reaction rate (case (a), figure 2). This, for instance, will be the case when the reactants are separated by a product layer of sufficient thickness.

The second reason is that for establishing a general law for a reaction it is also required that the solids involved in the diffusion be internally in equilibrium. The rate is primarily governed by the gradient of the chemical potential of the reacting particles, which potential is only defined when the particles in each single phase are arranged in such fashion that a state of minimum free energy is maintained within each phase throughout the course of the reaction. Only then is the reaction structure-insensitive. When the partaking phases are not in equilibrium internally, the rates become structure-sensitive and can be influenced to a large extent by incidental or deliberately created external conditions. The majority of solid-phase reactions are structure-sensitive, since solids usually contain enough non-equilibrium lattice disturbances to have a considerable effect on their chemical behavior. The energy required for motion of lattice defects or of particles influenced or created by lattice disturbances is lower than the migration energy of equilibrium particles.

Subsequently reaction mechanisms are discussed, first of solids internally in equilibrium, thereafter of the practically much more important reactions of non-equilibrium solids. The discussion of equilibrium crystals is limited to ionic crystals or to crystals whose building stones are at least ionic in nature. Only for such substances has an approximate but apparently adequate theory been developed. The mechanisms obtained offer also a qualitative basis for the understanding of reactions of non-equilibrium solids. In this case the reactions may be performed by motion of charged or of uncharged particles (53).

VI. THEORETICAL ASPECTS OF PARTICLE MOTION IN SOLIDS: STRUCTURE-INSENSITIVE REACTIONS

A. Empirical facts on diffusion and conductivity in crystals

A vast literature of experiments on diffusion and electric conduction in solid salts has been accumulated. The general results may be summarized as follows (4, 99, 110):

Diffusion in solid salts or in systems of solid salts occurs frequently, especially in temperature regions ranging from a few hundred degrees below the melting points up to the melting points of the salts. The diffusion obeys Fick's laws and may accordingly be investigated in experimental arrangements which permit the use of conveniently integrated forms of Fick's laws (4, 99).

Electrolytic conduction likewise occurs frequently in solid salts in the same temperature regions in which diffusion can be observed (147). This conduction yields important information about self-diffusion in crystals. Unlike conductance in solution, we may have in solids unipolar or bipolar conductivity. In the former instance the current is wholly transported by ions of one sign. By determining the transport numbers of the ions in a salt the mobile constituent or constituents are found, and the same kind of particles are the vehicle for the self-diffusion. Moreover, self-diffusion coefficients may be obtained approximately from the conductivity (23, 151, 156), for instance, by means of the Einstein relation: $D = k \times T \times B$, where D = diffusion coefficient, k = Boltzmann's constant, T = absolute temperature, and B = mobility of the ion in question. Otherwise, self-diffusion coefficients are not readily determined. In a few cases they have been measured directly with radioactive isotopes. In the case of lead iodide the self-diffusion coefficient of the lead ions has been measured directly and found to be in satisfactory agreement with the value calculated from the conductivity (69, 128). It is also possible to obtain a fair agreement for the diffusion coefficient of silver ions in silver chloride from measurements of the rate of exchange of radioactive silver ions (106) and from conductivity data (104).

The temperature coefficients of diffusion and of conductivity are always positive and can be represented by one or several expressions of the form:

$$D = A \exp(-Q/kT); \text{ respectively, } D = A_1 \exp(-Q_1/kT) + A_2 \exp(-Q_2/kT) + \cdots$$

$$\kappa = A'' \exp(-Q/kT); \text{ respectively, } \kappa = A_1'' \exp(-Q_1/kT) + A_2'' \exp(-Q_2/kT) + \cdots$$

where κ = the conductivity. It is noted that D and κ differ in the pre-exponential factors, whereas the Q-values representing energy terms are the same in both cases. An expression with two exponential terms is required for cases of bipolar conductivity, each term belonging to the motion of one kind of ion. A two-term expression appears furthermore in most instances of unipolar conductivity, owing to a rather sharp change of the temperature coefficient of the motion of the mobile ion. In this case the conductivity at higher temperatures invariably has larger A- and Q-values than has the conductivity at lower temperatures. Figure 5 illustrates this behavior for different specimens of silver bromide according to a recent investigation by Shapiro and Kolthoff (134). Silver bromide is a unipolar conductor (133, 147), the silver ion being the mobile constituent. Figure 5 also exhibits the characteristic fact that the high-temperature conductivity is fairly reproducible, whereas the low-temperature branch of the conductivity is structure-sensitive and varies from specimen to specimen or with different treatments of a given specimen. In the case of bipolar conductivity the corresponding behavior would yield a four-term expression. Analogous conditions prevail, of course, in diffusion.

Many solids exhibit pronounced electronic conductivity, and even the most perfect ionic conductors may under certain circumstances acquire a feeble electronic conductivity. Electronic conduction plays an important part in certain reactions in the solid state. In general it is structure-sensitive, the value of the conductivity being strongly affected by the presence of impurities or by deviations from the stoichiometric composition. Conduction in compounds is either really metallic or of a specific nature usually designated as semiconductivity, and occasionally either may occur in the same substance depending on the state of the specimen (Cu_2Se (123); Cu_2Te (122)). A comprehensive tabulation of electronic conductors and a tentative classification on the basis of electronic structure have recently been given by Meyer (109). Semiconductivity proper is characterized as follows (99, 130):

As in metals, the Hall effect is found in electronic conductors, the sign of the Hall coefficient, however, being positive or negative depending on the chemical nature of the substance. In some preparations of cuprous oxide a change of the sign of the Hall coefficient from negative to positive with increasing temperature has been observed (127).

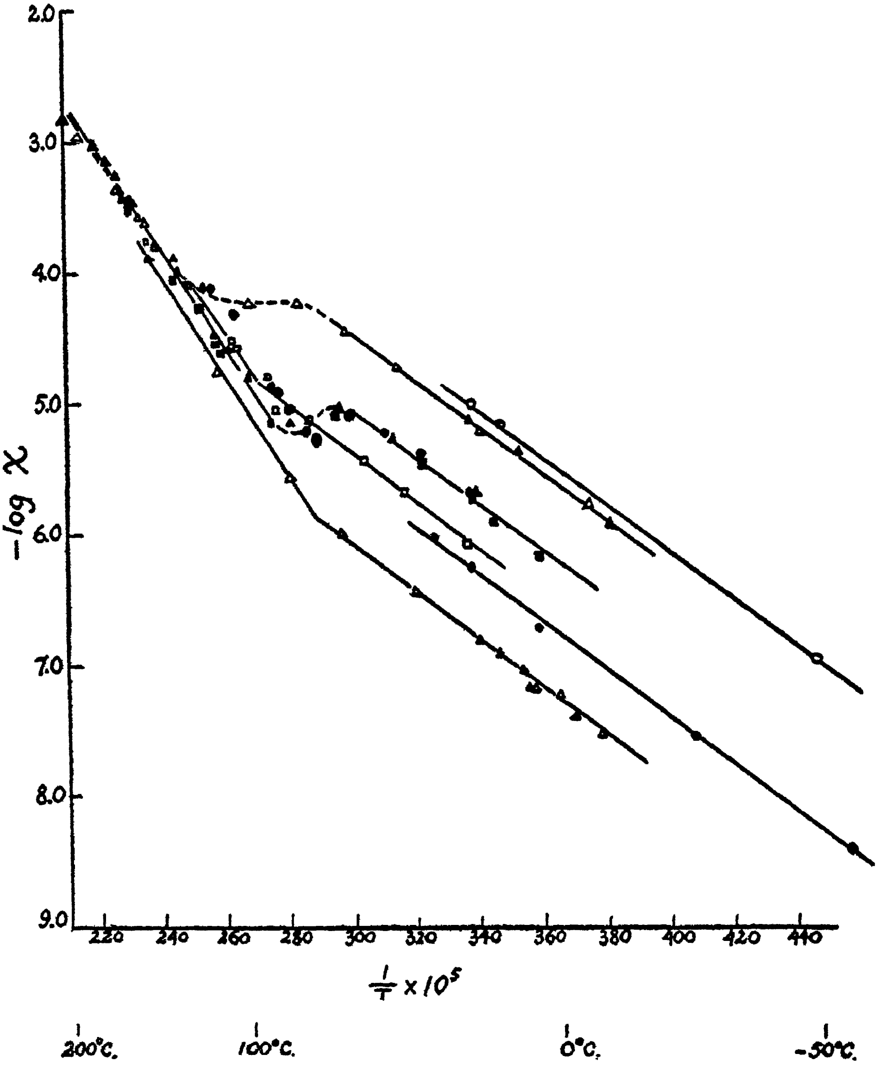

FIG. 5. Electrical conductivity of silver bromide (Shapiro and Kolthoff (134))

Also as in the case of metals, thermoelectric forces are developed in combinations of electronic conductors (159).

The temperature coefficient of semiconductivity is positive and follows an exponential expression of the form:

$$\kappa_\epsilon = A_\epsilon \exp(-Q_\epsilon/kT)$$

analogous to the temperature dependence of ionic conductivity. The values of A_ϵ and Q_ϵ vary greatly with the history of the specimen.

B. The state of solids being internally in equilibrium

A quantitative discussion must be limited to the reproducible (high-temperature) part of diffusion and conduction which apparently is structure-insensitive, in contrast to the poorly reproducible low-temperature motion. An adequate theoretical interpretation of the phenomena described is due primarily to Schottky and Wagner (126, 157, 164) after preliminary work by Frenkel (31), later extended by Jost (98, 100), Mott and Gurney (110), and others (9, 119). Schottky and Wagner showed that an ideal crystal at finite temperatures is in equilibrium only when a definite fraction of lattice particles have left their normal sites and are occupying certain positions of disorder. The possible states of disorder are pictured schematically in figure 6, showing a binary crystal of the composition MeX. The crystal in ideal order is illustrated in figure 6a. Figure 6b represents the possibility that ions of one sign have moved into interstitial positions (in the case of a cubic face-centered lattice most likely into the centers of the cubes), leaving an equal number of lattice sites vacant. Ions in interstitial positions are indicated by ○ and vacant lattice sites (holes) by □. In figure 6c both anions and cations occupy interstitial positions in equivalent numbers, in which case no vacant lattice sites need be formed. Figure 6d shows the occurrence of positive and negative lattice holes in equivalent numbers without any ions having had to move into interstitial positions. Figure 6e finally shows the possibility that anions and cations occupy wrong lattice sites in equivalent numbers.

In principle, all types of disorder may occur simultaneously. In ionic lattices the cases of figures 6c and 6e (interstitial disorder of ions of both signs without formation of lattice holes, and the interchange of lattice positions) are improbable for energetic reasons, but of practical importance are the cases of figure 6b (interstitial disorder of one kind of ions with equal number of lattice holes) designated as Frenkel disorder, and figure 6d (formation of lattice holes of both kinds of ions) designated as Schottky disorder. In Schottky disorder the ions which have left their lattice sites occupy additional layers of regular lattice points deposited at the surfaces of the crystals. Interchange of lattice positions may, however, occur in molecular or in metallic lattices.

Frenkel disorder is likely to occur when anion and cation of the crystal differ substantially in size, and when polarization of the lattice is strong. This is the case with silver chloride and bromide, where all evidence points to a Frenkel disorder of the silver ions (100, 104). Schottky disorder is favored when anion and cation are of similar size, and when polarization of the lattice is weak, as, for instance, with most alkali halides (100, 126). Usually the degree of disorder

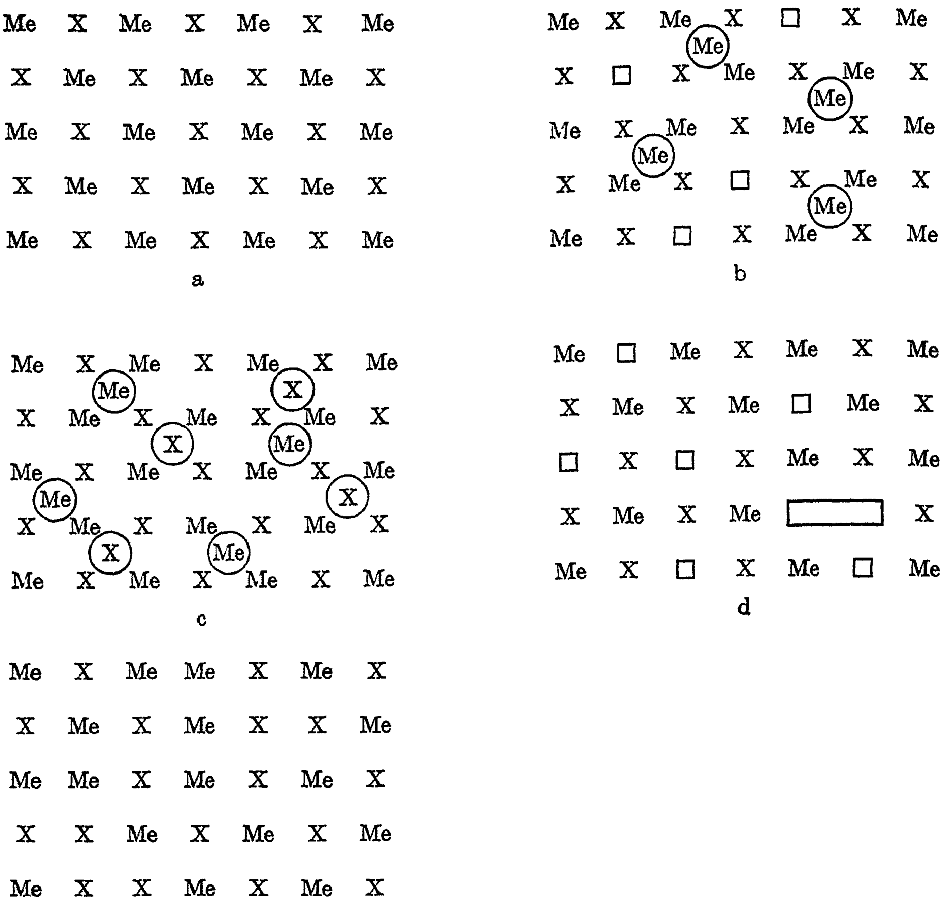

Fig. 6. Disorder models for a binary solid

is small, and the interaction between disordered particles can be neglected. Then the number of disordered ions (n) is, in a first approximation:

$$\text{For Frenkel disorder: } n \sim \sqrt{N^l N^0} \exp\left(-\tfrac{1}{2}E_F/kT\right) \tag{4a}$$

and

$$\text{For Schottky disorder: } n \sim N^l \exp\left(-\tfrac{1}{2}E_S/kT\right) \tag{4b}$$

where N^l = number of normal lattice positions,
N^0 = number of possible interstitial sites,
E_F = energy required to transfer an ion from its lattice position to an interstitial position, and
E_S = energy required to remove an ion pair from the interior of the crystal and to attach it at the outside as regular new lattice points.

It is to be noted that E_F and E_S represent heats of reaction. The thermodynamic lattice disorder is analogous, for instance, to the dissociation of a weak electrolyte in solution; every process of disorder creates two positions of disorder,—either an interstitial ion and a lattice hole, or two lattice holes. To give an idea of the degrees of disorder which may occur, the following tabulation has been compiled, assuming the reasonable value of 1 e.v. for the disorder energy and also that the number of interstitial positions available equals the number of normal lattice positions. With these assumptions the degree of disorder is the same for Frenkel and for Schottky disorder.

ENERGY OF DISORDER	DEGREE OF DISORDER: n/N^l AT						
	100°C.	200°C.	250°C.	300°C.	350°C.	400°C.	500°C.
1 e.v.	2×10^{-7}	5×10^{-6}	1.5×10^{-5}	4×10^{-5}	9×10^{-5}	2×10^{-4}	6×10^{-4}
For AgCl∼0.8 e.v.		7×10^{-5}	2.2×10^{-4}	5.5×10^{-4}	1.5×10^{-3}		
For AgBr∼0.8 e.v		6×10^{-4}	1.8×10^{-4}	4.0×10^{-3}			

For comparison purposes values for the degree of disorder of silver chloride and silver bromide as determined by Koch and Wagner in an indirect way (104) are added. Obviously the approximations (4a, 4b) yield values of reasonable magnitude. A complete calculation of the lattice disorder is not as yet possible (100, 111), mainly because of the difficulty of deriving the disorder energy from lattice data. Mott and Gurney (110) have considerably improved the approximation by taking into account the temperature dependence of the disorder energy and the disturbance of the lattice vibrations by the positions of disorder. They obtained for the number of disordered ions:

$$\text{For Frenkel disorder: } n \cong \sqrt{N^l N^0}/B\gamma_F \exp\left(-\tfrac{1}{2}E_{0_F}/kT\right) \tag{5a}$$

and

$$\text{For Schottky disorder: } n \cong N^l\, B\gamma_S \exp\left(-\tfrac{1}{2}E_{0_S}/kT\right) \tag{5b}$$

where E_{0_F} and E_{0_S} = the respective disorder energies at absolute zero temperature,
B = a factor with a numerical value of about 100,
γ_F and γ_S = factors which in case of a cubic crystal are of the order of 1, and 10–100, respectively.

The improvement introduced by expressions 5a and 5b is such that an approximate calculation of the pre-exponential factor in the temperature function of the ionic conductivity was possible.

There are a few compounds with a special form of Frenkel disorder. They include the high-temperature modifications of silver iodide (141), silver sulfide (121), and silver mercuric iodide Ag_2HgI_4 (101). There the anions possess a normal lattice, whereas the cations are distributed completely at random in the interstices of the anion lattice. The general theory outlined above is, of course, not applicable to these cases of disorder.

C. Mechanism of diffusion and conductivity

The particle motion in crystals giving rise to the establishment of internal equilibrium, or to diffusion, or to ionic conductivity is carried out by the disordered fraction of lattice particles. The possible modes of transport of matter in a crystal of the composition MeX are indicated by figure 7: (*a*) ions in interstitial positions move through the interstices; (*b*) ions move from normal lattice positions into the interstices while an equal number of vacant lattice sites are filled with ions leaving interstitial positions; (*c*) ions move from normal lattice positions into adjacent vacant sites eliminating the original holes and creating new holes. This process represents a migration of holes in the opposite direction.

In modes (b) and (c) there is a continuous exchange of moving particles, making possible a transfer of matter over distances much larger than the mean free path of the moving particles. In solids with Frenkel disorder all three modes of migration may occur simultaneously, whereas in substances with Schottky disorder only mode (c) is possible.

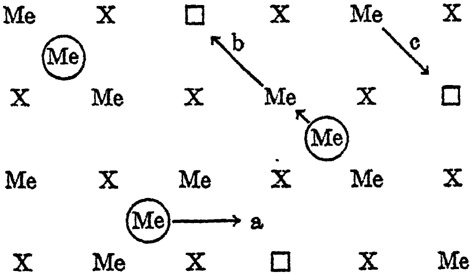

FIG. 7. Possibilities for ionic motion in a binary solid

The movement of ions within the interstices, from lattice positions to positions of disorder, or *vice versa*, requires activation energy. Only that fraction of the total number of disordered ions having the required activation energy (U) can overcome the potential barrier and move from one equilibrium position to the next one. Assuming, for the sake of simplicity, the same U-value for the different modes of migration of a given ion, the number of mobile particles becomes proportional to exp $(-(\frac{1}{2}E + U)/kT)$; the term $(\frac{1}{2}E + U)$ obviously equals the previously mentioned energy term Q appearing in the empirical temperature function of diffusion or conduction. The number of mobile particles given by exp $(-(\frac{1}{2}E + U)/kT)$ represents an equilibrium value, and processes depending on this number must be found to be reproducible. This holds for the high-temperature branch of ionic conductivity or diffusion which is often well reproducible. The low-temperature branch which is irregular and poorly reproducible must be ascribed to non-equilibrium caused by external conditions. The latter type of migration is discussed below.

A number of attempts have been made to derive theoretically or semiempirically the structure-insensitive part of the temperature function of diffusion or conductivity (11, 22, 98, 100, 139). A fruitful application of the disorder models has been made by Mott and Gurney (110), who calculated approximately the pre-exponential factor of ionic conductivity. In electric conduction the potential barrier for particle motion is decreased in the direction of the applied external field, and it is increased in the opposite direction. The net result is a drift of ions in the direction of the field which in the case of a binary cubic crystal is given by:

$$\kappa = N\,\frac{\epsilon^2 a^2}{kT}\,\nu CB\gamma \exp\left(-[\tfrac{1}{2}E_0 + U_0]/kT\right) \tag{6}$$

where the newly appearing symbols have the following meanings:

N = Avogadro's number,
ϵ = electronic charge,
a = lattice parameter (approximately),
ν = frequency of lattice vibrations,
C = factor with a numerical value of about 10, and
U_0 = activation energy of motion at absolute zero temperature.

Accordingly, the pre-exponential factor of the temperature function of conductivity is temperature dependent, which seems to be compatible with the experimental data available. For a temperature of 600°K. the pre-exponential factors for Frenkel disorder and for Schottky disorder can be estimated to be 3×10^5 and $3 \times 10^6 - 3 \times 10^7$, respectively. Actually, substances with Schottky disorder appear to possess larger pre-exponential factors than substances with Frenkel disorder. For instance, the pre-exponential in the empirical conductivity expression for sodium ions in sodium chloride having Schottky disorder is 1.4×10^6 (135), whereas that of silver ions in silver bromide having probably Frenkel disorder is 2×10^5 (104).

D. *Extension of disorder models for non-stoichiometric composition and for electronic disorder*

So far crystals of stoichiometric composition have been discussed. In reality the composition of solids is never strictly stoichiometric nor is it rigorously defined. The deviations are usually minute, but may reach substantial proportions in a number of substances (2). Particularly the products of reactions in the solid state must necessarily be of non-stoichiometric and of variable composition. For the diffusion of reactants through the product layers a gradient of the chemical potential is required, i.e., a variable composition of the product layers. The variation of the composition is made possible by a relative excess of the diffusing components which is largest at the phase boundary at which each component enters and which decreases towards the opposite phase boundary.

An excess of a component can be accommodated in two ways: by incorporating particles in a number greater than the number of regular lattice sites available, or in the form of a deficiency of some other constituent whose lattice, then, is incompletely occupied. The models by which the disorder states of stoichiometric compounds were described can readily be adapted for non-stoichiometric crystals. This is illustrated in figure 8, again for the binary crystal of over-all composition MeX. In Figure 8a the excess metal is contained in the crystal in interstitial solution, and the metal lattice may or may not still contain holes, which at any rate are less numerous than the interstitial cations. Figure 8b refers to the case where the excess metal occupies regular lattice positions of the anion lattice. As in the case of stoichiometric crystals this type of disorder is energetically improbable because of the strong repulsion of charges of equal sign in the lattice. Finally the excess metal may be present as an anion deficiency, which means holes in the anion lattice (figure 8c). In this case the cation lattice need not necessarily be completely occupied, but the number of cation holes, if any, is smaller than the equivalent number of anion holes.

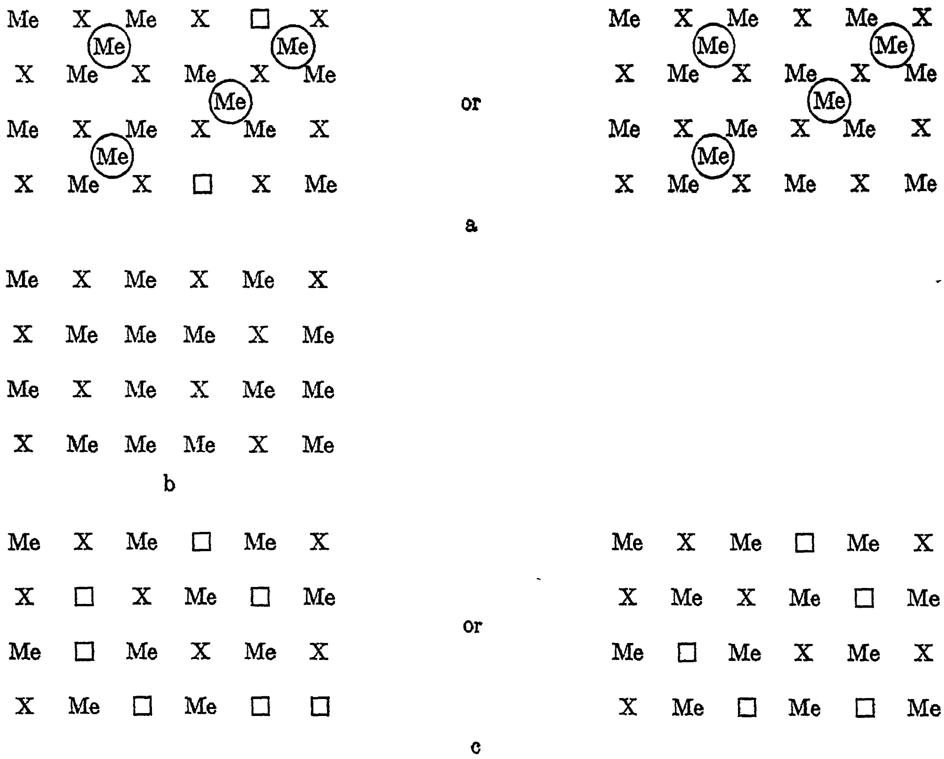

FIG. 8. Disorder models for a binary solid of non-stoichiometric composition

In principle, continuous transition is possible from non-stoichiometric to stoichiometric composition. The disorder models permit a continuous transition from the case of figure 8a to pure Frenkel disorder, or from the case of figure 8c to pure Schottky disorder. Therefore, no discontinuous change of the properties of a solid is observed when the composition undergoes such transition. The only differentiation is that in stoichiometrically composed substances one kind of disordered particles must be balanced by an equivalent number of another kind of disorder, for instance, interstitial ions by lattice holes of the same sign, whereas such a condition does not apply to non-stoichiometric substances.

Electronic disorder: For the interpretation of electronic conductivity a mechanism can be formulated analogous to that of ionic conductivity based on the assumption of disordered electrons, which may be present as semi-free "interstitial" electrons or as missing electrons, "electron holes" which are equivalent to positive charges.[3] For a stoichiometric substance an equilibrium reaction:

$$\text{Ordered lattice} \rightleftharpoons \text{semi-free electron} + \text{electron hole}$$

may be postulated. Figure 9a shows schematically how such electronic disorder might be realized in the case of cuprous oxide. Interstitial, semi-free electrons are symbolized by $\textcircled{\varepsilon}$ and electron holes by $\boxed{\varepsilon}$. Electron holes could be assumed to be present as doubly charged copper ions. Electronic conduction is accomplished by the motion of interstitial electrons, or by electron transfer from neighboring ions to electron holes filling the original holes and creating new holes. It is this hole migration which gives rise to the positive Hall effect. Actually, appreciable electronic disorder of stoichiometric compounds is very rare and would usually be realized only at high temperatures. Since, however, solids are never of entirely stoichiometric composition, electronic disorder must occur at all temperatures in order to neutralize the excess charge introduced into the lattice by the excess, or by the deficiency, of one of the constituent ions. Thus an accompanying electron excess conductivity, or electron hole conductivity, is made possible which is discussed in more detail in a subsequent section. In figure 9b the actual conditions are shown schematically for cuprous oxide. Cuprous oxide contains an excess of oxygen ions in the form of an incompletely occupied lattice of cuprous ions (18). The charges of oxygen ions which are not balanced by cuprous ions are neutralized by the electron holes.

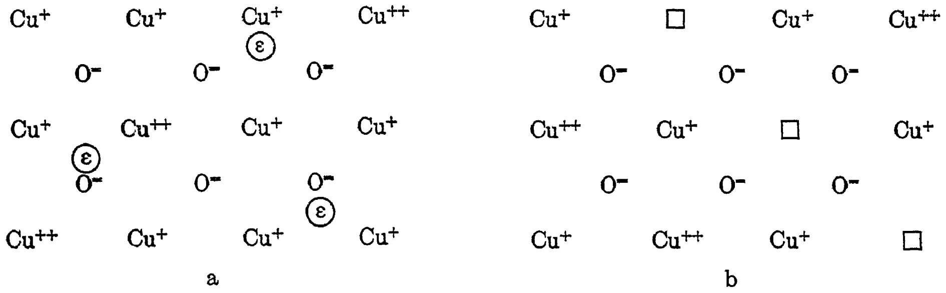

FIG. 9. Disorder model for cuprous oxide (Dünwald and Wagner (18))

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[3] In the present discussion of the electronic states in crystals the band approximation (109, 110, 130) is not introduced. It has been shown, particularly by Wagner (157b, 160), that corpuscular electronic models are satisfactory for the description of reactions in the solid state. For finer details and for an understanding of processes like photoconductivity, photoelectricity, photochemistry, etc., the band approximation would be required.

Owing to this state of affairs the electronic conductivity of cuprous oxide takes place as electron hole migration, and the ionic conductivity as migration of holes of cuprous ions.

The amount of excess oxygen taken up by cuprous oxide is determined by temperature and pressure. At constant temperature the equilibrium between gaseous oxygen and cuprous oxide is expressed by the equation:

$$O_{2(\text{gas.})} + 4\text{Cu}^{+}_{\text{lattice}} + 4\epsilon_{\text{lattice}} \rightleftharpoons 2\text{Cu}_2\text{O}_{\text{lattice}} + 4\boxed{\text{Cu}^{+}} + 4\boxed{\varepsilon}$$

Dünwald and Wagner (18) have shown that the law of mass action can be applied to reactions of this kind:

$$K_T = \frac{(\text{Cu}_2\text{O}_{\text{lattice}})^2 \times (\boxed{\text{Cu}^{+}})^4 \times (\boxed{\varepsilon})^4}{p_{O_2} \times (\text{Cu}^{+}_{\text{lattice}})^4 \times (\epsilon_{\text{lattice}})^4} \tag{7}$$

where p_{O_2} = partial pressure of oxygen. Since the concentrations of ordered cuprous ions, and also of ordered cuprous oxide, and of ordered electrons remain practically unchanged in the reaction, equation 7 reduces to:

$$K'_T = \frac{(\boxed{\text{Cu}^{+}})^4 \times (\boxed{\varepsilon})^4}{p_{O_2}} \tag{7a}$$

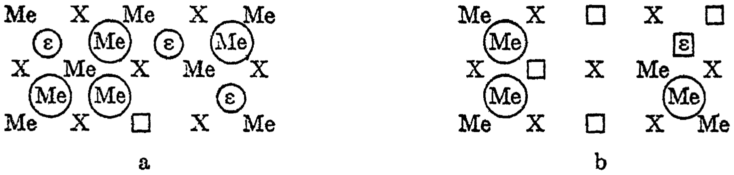
E. Experimental methods for determining the types of disorder

In cases of gross deviations from the stoichiometric composition the type of disorder can be found directly. The excess constituent is determined analytically. Comparison of the measured density with that calculated from x-ray data shows whether the excess constituent is incorporated interstitially, is present in the form of holes of the other constituent, or has entered by substitution. For instance ferrous oxide, which has the sodium chloride structure, can contain excess oxygen up to the composition $\text{FeO}_{1.09}$, this oxygen being present in the form of holes in the ferrous-ion lattice (97).

In substances of closely stoichiometric composition a direct determination of the disorder type appears hardly feasible (129, 163). Indirect and rather complicated methods must be applied, and relatively few compounds have been classified so far. In the case of sodium chloride an analysis of the energy conditions by Jost (100a) showed the presence of Schottky disorder. Jost (99) has further suggested the determination of disorder types by measuring the time interval in which the equilibrium changes from one state to another upon a sudden change of the temperature of the solid. In the case of Frenkel disorder the equilibrium change involves particle motion over atomic distances only, which would take place practically instantaneously; with Schottky disorder, the equilibrium change involves diffusion of lattice particles from the interior to the surface, or *vice versa,* which should require measurable times when the crystals are not too small. This promising method has not yet been applied.

Wagner (157b) has devised a procedure to detect disorder types, by which conclusions are drawn from the nature of the ionic and electronic conductivities of a given substance and from their dependence on the composition. Since the variation of the chemical composition cannot be determined directly, the substances are equilibrated with the vapor of a volatile (mostly the negative) constituent, and the dependence of the ionic and electronic conductivities on the vapor pressure is determined. The procedure may be illustrated by two examples:

(*1*) The substance investigated conducts predominantly electronically (transport number of electrons practically unity) and has in addition a weak cationic conductivity (transport number $\ll 1$), whereas the anions do not contribute to the conduction. With increasing partial pressure of the negative constituent, both the electronic and the ionic conductivity decrease. The substance, therefore, has the following disorder type (figure 10a). Excess cations are incorporated interstitially together with an equivalent amount of interstitial electrons. Current is conducted by these excess particles. The anions, being unable to move, have a perfectly ordered lattice. With increasing partial pressure of the negative component the excess cations and the interstitial electrons are increasingly used up to form a regular lattice owing to the equilibrium:



a

b

FIG. 10. Illustration of Wagner's method to determine types of disorder

$$X_{gas.} + \text{\textcircled{Me}} + \text{\textcircled{ε}} \rightleftarrows MeX_{lattice}$$

This reaction conforms to the observed pressure dependence of the conductivity. Zinc oxide and cadmium oxide at elevated temperatures are examples of this type of disorder (5).

(*2*) The substance in question is predominantly an ionic conductor, the cations being the mobile constituent (transport number practically unity). Besides, there is a weak electronic conductivity (transport number $\ll 1$), but no anionic conductivity. The electronic conductivity increases markedly with increasing partial pressure of the non-metallic component, whereas the ionic conductivity is practically pressure-independent. From these facts the following disorder type is derived (figure 10b). The substance possesses Frenkel disorder of the cations containing a slight excess of the non-metallic component which is accommodated in the form of extra cation holes together with the equivalent number of electron holes. Conduction is carried out by the disordered fraction of cations (interstitial cations and cation holes) and by the electron holes. If the substance were of stoichiometric composition, the number of interstitial ions would equal the number of ion holes: $\text{\textcircled{Me}} \rightleftarrows \boxed{Me}$ This is also approximately true in the actual non-stoichiometric compound, since it conducts predominantly ionically; this shows that the deviations from the stoichiometric composition are small compared with the total degree of disorder. Therefore, the ionic conductivity is practically independent of the slight changes of composition resulting from changes of the partial pressure of the negative component. The electronic conductivity, however, increases strongly under these conditions because the number of unbalanced cation holes and electron holes is increased by the reaction:

$$X_{\text{gas.}} + \textcircled{\text{Me}} + \boxed{\text{Me}} \rightleftarrows \text{MeX}_{\text{lattice}} + \boxed{\text{Me}} + \boxed{\varepsilon}$$

This type of disorder probably occurs in silver chloride and silver bromide and is discussed in a subsequent section.

Using the same reasoning, types of disorder other than those discussed may be identified. It also becomes evident from the examples described that an excess constituent is not necessarily the mobile component in a given compound or the vehicle for diffusion and reaction.

Another method for detecting the type of electronic disorder from the sign of the thermoelectric force of a couple made from the same bulk material but with different conductivity values has been devised by Wagner (159).

F. Application of the disorder theory to reactions in the solid state

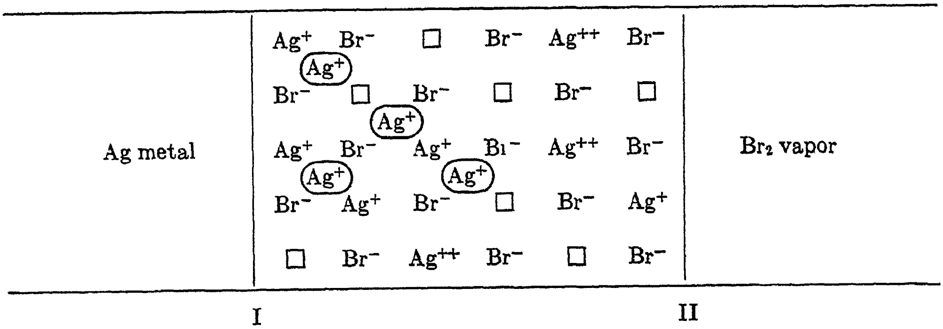
A good example of the applicability of the disorder theory may be found in the tarnishing of silver by chlorine or by bromine. Upon exposure to the halogen vapors, silver becomes covered with a coherent halide layer which steadily increases at elevated temperatures by diffusion of reactants through the layer. It was just stated that silver chloride and bromide show Frenkel disorder of the cations and may take up excess halogen with formation of ordered silver halide and electron holes. From this disorder type the following mechanism of tarnishing is derived. Assume that a crystal of silver bromide (or chloride) is exposed at one of its surfaces to bromine (or chlorine) vapor of such pressure that the crystal is not in equilibrium with the halogen vapor; under these conditions bromine vapor reacts with interstitial silver ions with the formation of fresh layers of silver halide and of electron holes, according to the equation:

$$\text{Br}_{2\text{gas.}} \rightleftarrows \text{Br}_{2\text{adsorbed}} + 2\textcircled{\text{Ag}^+} + 2\epsilon_{\text{lattice}} \rightleftarrows 2\text{AgBr}_{\text{lattice}} + 2\boxed{\varepsilon} \qquad (8)$$

The electron holes may reasonably be assumed to be present in the form of doubly charged silver ions. Interstitial silver ions, being depleted near the exposed surface owing to the reaction, are replaced by interstitial silver ions diffusing from the interior towards the exposed surface, whereas the resulting electron holes diffuse away from the reaction zone into the interior. The reaction proceeds until equilibrium of the entire crystal with halogen vapor at given temperature and pressure is established. Analysis of different sections of the crystal

—if it were feasible—would reveal throughout the crystal a uniformly distributed excess of halide ions as a result of the migration of silver ions and of electron holes.

This state of equilibrium is not established when the face of the halide crystal opposite to the surface exposed to halogen vapor is in contact with metallic silver, as is the case in tarnishing. Then, silver atoms from the metal phase cross the phase boundary and enter the halide phase in the form of interstitial silver ions and of semi-free electrons. The latter are immediately used up in neutralizing the electron holes arriving from the exposed surface layer, whereas the newly incorporated interstitial silver ions diffuse toward the exposed surface, there to continue the reaction. In this way the concentration gradients required for the diffusion of interstitial cations and for the motion of electron holes are continuously maintained so that the tarnishing reaction proceeds. This mechanism is illustrated in figure 11.



Phase boundary processes:

At I: $2Ag_{metal} + 2\boxed{\varepsilon} \rightleftarrows 2\enclose{circle}{Ag^+}$

At II: $Br_2 + 2\enclose{circle}{Ag^+} + 2\epsilon_{lattice} \rightleftarrows 2AgBr_{lattice} + 2\boxed{\varepsilon}$

Diffusion processes:

$\enclose{circle}{Ag^+}$ from I to II

$\boxed{\varepsilon}$ from II to I

Net reaction: $2Ag + Br_2 \rightarrow 2AgBr$

FIG. 11. Schematic mechanism of the reaction between silver and bromine

The mechanism[4] described is supported by the following quantitative relations developed by Wagner (158). Wagner has treated the tarnishing of metals in a general way. His basic assumption was that in a tarnishing system anions, cations, and electrons may be encountered as moving particles depending on the specific disorder type of the salt formed. In the silver halides migration of anions is not possible, but such might occur in other cases, for instance, in substances with Schottky disorder. The reaction rate is given by the absolute values of the flow (f) of particles through the diffusion layer:

$$dn/dt = |f_{\text{anion}}| + |f_{\text{cation}} = |f_{\text{electron}}$$

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[4] A fairly direct proof for such a mechanism has recently been given by Bardeen, Brattain, and Shockley (3) for the high-temperature oxidation of copper by means of radioactive copper tracers.

With the condition that space charges are not allowed to be formed in the salt by the motion of charged particles, and with the assumption that the phase boundary processes are so rapid that equilibrium is continuously established at the interfaces between metal and salt and between salt and non-metal, the reaction rate becomes:

$$\begin{aligned}\frac{\mathrm{d}n}{\mathrm{d}t} &= \frac{A}{\xi} \times \frac{300}{96{,}500} \times \frac{1}{N\epsilon} \times \int_{\text{Interface MeX/X}}^{\text{Interface Me/MeX}} \frac{(t_{\text{cation}} + t_{\text{anion}}) \times t_{\text{electron}}}{|z_{\text{cation}}|}\, \kappa\, \mathrm{d}\mu_{\text{Me}} \\ &= \frac{A}{\xi} \times \frac{300}{96{,}000} \times \frac{1}{N\epsilon} \times \int_{\text{Interface MeX/Me}}^{\text{Interface X/MeX}} \frac{(t_{\text{cation}} + t_{\text{anion}}) \times t_{\text{electron}}}{|z_{\text{anion}}|}\, \kappa\, \mathrm{d}\mu_{\text{X}} \qquad \text{(9a)}\end{aligned}$$

where the newly appearing symbols are:

$\mathrm{d}n/\mathrm{d}t$ = particle flow (in equivalents per centimeters per second),
A = cross section of diffusion layer (in cm.^{2}),
ξ = thickness of diffusion layer (in centimeters),
z = valence of ion in question, and
μ = chemical potential (per gram-equivalent).

Comparison with the previously given rate equation (1b, page 537), $\mathrm{d}n/\mathrm{d}t = A/\xi \times k$, shows that the rate constant (k) is given by the last three terms of equation 9a.

For an integration of equation 9a it is necessary to derive the relationship between the partial conductivities (i.e., the number of mobile particles) and the chemical potential in the crystal. However, since the deviations from the stoichiometric composition are usually minute, average values for the partial conductivities may be taken:

$$\begin{aligned}\frac{\mathrm{d}n}{\mathrm{d}t} &= \frac{A}{\xi} \times \frac{300}{96{,}500} \times \frac{1}{N\epsilon} \times \frac{(\bar{t}_{\text{cation}} + \bar{t}_{\text{anion}}) \times \bar{t}_{\text{electron}}}{|z_{\text{cation}}|}\, \bar{\kappa}\left[\mu_{\text{Me}}^{\text{Me/MeX}} - \mu_{\text{Me}}^{\text{MeX/X}}\right] \\ &= \frac{A}{\xi} \times \frac{300}{96{,}500} \times \frac{1}{N\epsilon} \times \frac{(\bar{t}_{\text{cation}} + \bar{t}_{\text{anion}}) \times \bar{t}_{\text{electron}}}{|z_{\text{anion}}|}\, \bar{\kappa}\left[\mu_{\text{X}}^{\text{X/MeX}} - \mu_{\text{X}}^{\text{MeX/Me}}\right]\end{aligned} \qquad \text{(9b)}$$

The bars over the symbols denote the average values. This relation is most conveniently applied when the difference of the chemical potential across the diffusion layer is measured as the E.M.F. (E_0) of a suitable galvanic element, for instance, in the chain

Me/MeX–suitable electrolyte (borax)–X (of the same pressure as in tarnishing)/suitable electrode (Pt)

The following equation is obtained:

$$\frac{\mathrm{d}n}{\mathrm{d}t} = \frac{A}{\xi} \times \frac{(\bar{t}_{\text{cation}} + \bar{t}_{\text{anion}})\bar{t}_{\text{electron}}}{F}\, \bar{\kappa} E_0 = \frac{A}{\xi} \times k \qquad \text{(9c)}$$

where F = Faraday's constant.

Before continuing with the discussion of the tarnishing of silver by chlorine or bromine, the applicability of equation 9c may be shown by the results obtained in other systems, as summarized in table 3.

It should be noted that equations 9 contain an expression for the product of ionic and electronic conductivities of the salt formed; tarnishing, therefore, is not possible when either kind of conductivity is missing in the reaction product. This explains the resistance of aluminum or beryllium or alloys containing aluminum or beryllium to oxidation (72), the ionic conductivity in aluminum oxide and in beryllium oxide being exceedingly small.

It is worth noting that the rate of tarnishing may be employed to determine electronic conductivities which are too small to be measured directly. This is illustrated by the last example of table 3, namely, the tarnishing of silver by iodine. Precise measurements of the conductivity of silver iodide yielded a transport number of unity for the cations within 1 per mille (148); the transport number of electrons, therefore, must be smaller than 10^{-3}, a figure which is confirmed by the value of about 10^{-4} calculated from the measured rate of tarnishing.

TABLE 3

Rate of tarnishing reactions

SYSTEM	TEMPERATURE	RATE CONSTANT (EQUIV./CM.SEC.)		REFERENCES
		Observed	Calculated	
$Ag + S_{liquid} \rightarrow \alpha\text{-}Ag_2S$	220	1.6×10^{-6}	$2\text{–}4 \times 10^{-6}$*	(158)
$Cu + I_2 \rightarrow \gamma\text{-}CuI$	195	3.4×10^{-10}	3.8×10^{-10}	(113)
$Cu + O_2 \rightarrow Cu_2O$	1000	7×10^{-9}	6×10^{-9}	(18)
$Ag + I_2 \rightarrow \alpha\text{-}AgI$	200	1.13×10^{-9}	$t_{electron}$: $\sim 10^{-4}$	(124)

* Variation due to different values given for the conductivity of Ag_2S.

In most tarnishing reactions the mechanism is more complex, so that the rate expressions 9 no longer apply quantitatively, one of the reasons being that the rate of phase boundary processes might contribute to the over-all rate. This seems to be the case in the tarnishing of silver by gaseous sulfur or by hydrogen sulfide (124). Other reasons are mentioned below.

So far the derivation of the tarnishing rate was merely based on the assumption of ions and electrons as the moving particles, without involving any of the specific models of the disorder theory. Wagner (160) has shown with the example of the tarnishing of silver by chlorine or bromine that the integral in equation 9a can be evaluated to a better approximation by making use of the individual models of the disorder theory.

Each volume element of the layer of silver halide can be considered as being in equilibrium with gaseous halogen at a certain pressure (p_X). Assuming ideal behavior, equation 9a changes to:

$$\frac{dn}{dt} = \frac{A}{\xi} \times \frac{300}{96{,}500} \times \frac{RT}{N\epsilon} \times \int_{\text{Interface MeX/Me}}^{\text{Interface X/MeX}} \frac{(t_{cation} + t_{anion})t_{electron}}{|z_{anion}|} \kappa \, d \ln p_X \qquad (9d)$$

According to the probable disorder model of silver chloride and bromide, the cationic conductivity is practically independent of the halogen pressure (transport number approximately unity), the anionic conductivity is zero, and the dependence of the electronic conductivity on the halogen pressure can be obtained from the equilibrium constant (K) of the phase boundary reaction (equation 8, page 554):

$$K = \frac{(\boxed{\varepsilon})}{(\enclose{circle}{\mathrm{Ag^+}})^2 \times p_\mathrm{X}} \tag{10}$$

The lattice particles which partake in the reaction do not appear in the equilibrium relation, since their concentrations remain practically constant in the reaction. The concentration of electron holes is:

$$(\boxed{\varepsilon}) = K'(\enclose{circle}{\mathrm{Ag^+}}) \times p_\mathrm{X}^{1/2}$$

Because the ionic conductivity is independent of the halogen pressure, the total disorder is much greater than the disorder caused by excess halogen $(\boxed{\varepsilon}) \ll (\enclose{circle}{\mathrm{Ag^+}})$, so that:

$$(\boxed{\varepsilon}) \sim K'' \times p_\mathrm{X}^{1/2}$$

The electronic conductivity is proportional to the concentration of electron holes:

$$\kappa_\epsilon = C \times p_\mathrm{X}^{1/2}$$

respectively:

$$\kappa_\epsilon = \underset{\text{at } p_\mathrm{X}=1}{\kappa_\epsilon} \times p_\mathrm{X}^{1/2}$$

Thus the reaction rate is given by:

$$\begin{aligned}\frac{dn}{dt} &= \frac{A}{\xi} \times \frac{300}{96{,}500} \times \frac{RT}{N\epsilon}\underset{\text{at } p_\mathrm{X}=1}{\kappa_\epsilon} \int_{\text{Interface MeX/Me}}^{\text{Interface X/MeX}} p_\mathrm{X}^{1/2}\, d \ln p_\mathrm{X} \\ &= \frac{A}{\xi} \times \frac{600}{96{,}500} \times \frac{RT}{N\epsilon}\underset{\text{at } p_\mathrm{X}=1}{\kappa_\epsilon} \left(\overset{\mathrm{X/MeX}}{p_\mathrm{X}^{1/2}} - \overset{\mathrm{MeX/Me}}{p_\mathrm{X}^{1/2}} \right)\end{aligned} \tag{9e}$$

The halogen pressure with which the reaction product is in equilibrium at the contact zone with silver is negligibly small, therefore equation 9e reduces to:

$$\frac{dn}{dt} = \frac{A}{\xi} \times \frac{600}{96{,}500} \times \frac{RT}{N\epsilon}\underset{\text{at } p_\mathrm{X}=1}{\kappa_\epsilon} \times p_\mathrm{X}^{1/2} = \frac{A}{\xi} \times k \tag{9f}$$

A complete evaluation of equation 9f is not yet possible, since the electronic conductivity of silver chloride and bromide has not yet been measured directly at any halogen pressure. But the validity of equation 9f was demonstrated by

Wagner, who measured the tarnishing rate of silver by bromine and chlorine at various halogen pressures. The results, given in table 4, show satisfactory agreement between the observed ratios of rate constants with the theoretical ratios. It is to be expected that deviations increase with increasing temperatures because equation 9f, based on concentrations rather than on activities, must fail at the greater degrees of disorder which exist at higher temperatures. The total conductivity of silver bromide in equilibrium with bromine of 0.23 atm. at 200°C. was found to be 12 per cent larger than in an atmosphere of pure nitrogen. It is of interest to compare this figure with the value of the electronic conductivity calculated by Wagner from the observed rate constants and from the conductivity values determined by Tubandt and Lorenz (149) in an atmosphere of nitrogen. The data are given in table 5; at a temperature of 200°C. an electronic contribution of 17 per cent to the total conductivity is obtained. All evidence, therefore, points to the disorder type described for silver chloride and bromide.

TABLE 4

Tarnishing of silver by chlorine and bromine

Silver and chlorine

TEMPERATURE	$k_{\text{observed}} \times 10^{10}$			$\frac{k_{0.04}}{k_{1.00}}$	$\frac{k_{0.17}}{k_{1.00}}$
	p_{Cl_2} (atm.)				
	0.04	0.17	1.00	THEORETICAL, 0.2	THEORETICAL, 0.41
°C.					
300			0.19		
350	0.16	0.34	0.82	0.20	0.41
400	0.35	0.70	2.06	0.17	0.34

Silver and bromine

TEMPERATURE	$k_{\text{observed}} \times 10^{10}$		$\frac{k_{0.09}}{k_{0.23}}$	
	p_{Br_2} (atm.)			
	0.09	0.23	THEORETICAL, 0.62	
°C.				
200	0.23	0.38	0.61	
250	0.53	0.91	0.58	
300	0.96	1.78	0.54	
350	1.21	2.32	0.52	
400	1.15	2.27	0.50	

The tarnishing of metals has been discussed in some detail in order to demonstrate that reactions in the solid state may require the migration of ions and electrons. When reactions take place between ionic compounds and not between metals and non-metals, a movement of ions alone may suffice to make the reaction possible. As an example of such a mechanism we may consider the reaction:

$$MeX_m + Me'X_n \rightarrow MeMe'X_{m+n}$$

which can proceed by movement of ions of one kind only: namely, the cations moving through the product layer in opposite directions and reacting at the phase boundaries with the further formation of new product. The over-all mechanism is illustrated in figure 12. The mechanism by which the cations actually travel is, of course, given by the specific disorder type of the reaction product. The concentration gradients required for the diffusion are maintained by the continuous flow of cations from the reactants into the product layer.

TABLE 5

Electronic conductivity in silver bromide

TEMPERATURE	$\kappa_{\text{AgBr in N}_2}$	κ_{electron} FROM k IN 0.23 ATM. OF Br_2	t_{electron}
°C.			
200	5.2×10^{-4}	9.0×10^{-5}	0.17
250	3.2×10^{-3}	2.0×10^{-4}	0.06
300	1.8×10^{-2}	3.5×10^{-4}	0.02
350	8×10^{-2}	4.2×10^{-4}	0.005
400	3.8×10^{-1}	3.8×10^{-4}	0.001

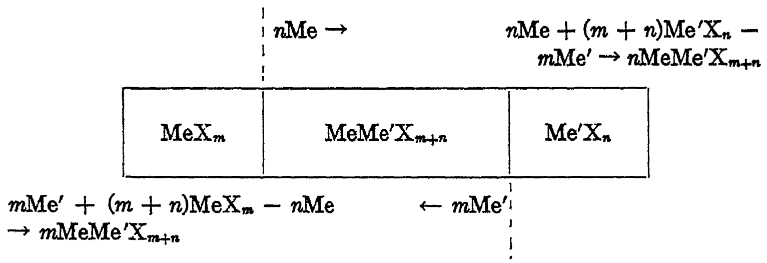
nMe →
nMe + (m + n)Me′Xₙ − mMe′ → nMeMe′Xₘ₊ₙ
MeXₘ
MeMe′Xₘ₊ₙ
Me′Xₙ
mMe′ + (m + n)MeXₘ − nMe → mMeMe′Xₘ₊ₙ
← mMe′

FIG. 12. Schematic mechanism of double salt formation from two cationically conducting salts (Wagner (161)).

The reaction rate has been calculated by Wagner (161), comparable to his treatment of tarnishing reactions, by deriving the total flow of particles through the diffusion layer:

$$\frac{dn}{dt} = \frac{A}{\xi} \times \frac{300}{96{,}500} \times \frac{1}{N\epsilon} \int_{\text{Interface MeMe}'\text{X}_{m+n}/\text{Me}'\text{X}_n}^{\text{Interface MeX}_m/\text{MeMe}'\text{X}_{m+n}} \frac{t_{\text{Me}} \times t_{\text{Me}'}}{t_{\text{Me}} + t_{\text{Me}'}} \kappa \frac{(\text{Me}) + (\text{Me}')}{(\text{Me}')} \, d\mu_{\text{MeX}_m} \tag{11a}$$

where the concentrations of cations (( )) in the diffusion layer are expressed in equivalents per cm.³ In nearly stoichiometric compounds average values may again be taken for the partial conductivities and the concentrations. Expressing the free energy of formation by the E.M.F. (E_0) measured with a suitable galvanic chain, equation 11a becomes:

$$\frac{dn}{dt} = \frac{A}{\xi} \times \frac{\bar{t}_{\text{Me}} \times \bar{t}_{\text{Me}'}}{\bar{t}_{\text{Me}} + \bar{t}_{\text{Me}'}} \times \frac{\bar{\kappa}}{F} \times \frac{\overline{(\text{Me})} + \overline{(\text{Me}')}}{\overline{(\text{Me}')}} \times E_0 = \frac{A}{\xi} \times k \tag{11b}$$

Equation 11b has been verified by Koch and Wagner (103) for the reaction:

$$2AgI + HgI_2 \rightarrow Ag_2HgI_4$$

which takes place by diffusion of silver ions and mercuric ions. The observed rate constant of 2.1×10^{-11} equiv./cm. × sec. agreed well with the calculated value of 1.9×10^{-11}.

Similarly, the rates of other reactions between ionically conducting compounds may be calculated.

VII. STRUCTURE-SENSITIVE REACTIONS

A. *Limitations of the applicability of the disorder theory*

While the basic principle that diffusion and reaction in the solid state are performed by the disordered fraction of lattice particles in the system apparently applies to all cases, the quantitative applicability of the disorder theory is limited, and experimental proofs have so far been established only for the reactions given in the preceding section. One or more of the following reasons may be responsible for this state of affairs.

(*1*) *Influence of phase boundary processes:* Theoretically the influence of phase boundary processes might always be eliminated by proper selection of the dimensions of the reacting systems. In many practical and technically important cases, however, where the diffusion is sluggish the reactions have to be carried out with fine powder mixes in which the diffusion layers are very thin, so that phase boundary processes may become important or even predominant.

(*2*) *Structure-sensitive factors:* It has been mentioned previously that the reproducible branch of the temperature function of conduction or diffusion frequently changes rather abruptly at some lower temperature into a poorly reproducible structure-sensitive branch (figure 5). The reason for this is that solids can easily change into thermodynamically unstable states in which the solids are imperfect and are in an abnormally energy-rich (active) state. Various kinds of imperfections may occur. They may, for example, be identical with the thermodynamic lattice disorder, but be present in a number larger than is required by the equilibrium. Or the imperfections may occur in the form of unstable modifications or unstable solid solutions, expanded or deformed lattices, holes or cracks of atomic dimensions, irregular displacement of lattice particles, crystallite sizes of colloidal dimensions, amorphous state. Despite their instability, such imperfections may exist for long periods of time, indeed sometimes indefinitely when the particle motion leading to internal equilibrium (thermal aging) is completely frozen. The probability of a removal of the faulty state by rearrangement increases exponentially with increasing temperature; therefore the transition from the migration of lattice imperfections to the thermodynamic lattice diffusion may frequently be observed as a sharp break in the temperature function of diffusion or conductivity. But on the other hand it is possible that the imperfect state of the solid persists at all temperatures to such an extent that the thermodynamic diffusion remains obscured.

The presence of an excess of one or more constituents in the products of reactions in the solid state may further increase and also stabilize the lattice imperfections.

The slope of the low-temperature branch of conduction and diffusion is smaller than the slope of the high-temperature branch, since for the motion of lattice imperfections along cracks, through holes, and at any internal surface activation energy alone is required, whereas the energy requirements of the high-temperature motion include both activation energy and disorder energy ($\frac{1}{2}E + U$, *cf.* page 548). The lattice imperfections are thus able to move with a mechanism somewhat similar to zeolithic diffusion, but their thermal energy is not sufficient for an interaction with ordered lattice particles which would gradually eliminate the imperfections. The concentration, and probably also the qualitative nature, of the imperfections are sensitive to external and frequently uncontrolled conditions and may vary from specimen to specimen. For this reason the low-temperature motion is poorly reproducible.

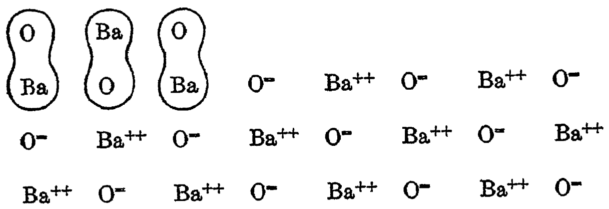
O Ba Ba O O Ba O⁻ Ba⁺⁺ O⁻ Ba⁺⁺ O⁻
O⁻ Ba⁺⁺ O⁻ Ba⁺⁺ O⁻ Ba⁺⁺ O⁻ Ba⁺⁺
Ba⁺⁺ O⁻ Ba⁺⁺ O⁻ Ba⁺⁺ O⁻ Ba⁺⁺ O⁻

FIG. 13. Schematic picture of formation of surface molecules on barium oxide (De Boer (9))

Imperfect solids may be formed in other ways than by reactions in the solid state, for instance, by precipitation from solution, by rapid quenching of melts, by preparation at relatively low temperatures (decomposition), by electrochemical processes, by incorporation of small amounts of impurities, and by mechanical treatment.

(3) *Uncharged particles as vehicle of reaction:* Many reactions have been observed to occur with great intensity at temperatures at which the reacting system does not possess an ionic conductivity adequate to explain the mechanism as a motion of ions. A detailed mechanism of the motion of uncharged particles on the basis of the general disorder theory has not yet been developed and certainly would be very difficult to prove experimentally. There is also some likelihood that the motion of uncharged particles does not proceed by a thermodynamically determined mechanism, but rather by diffusion through lattice imperfections, since neutral atoms or neutral combination of atoms may be too large to diffuse interstitially or through lattice holes of the reaction product.

Mobile uncharged particles may be formed in solids whose building stones are ions, but which do not exhibit ionic conductivity. It appears possible that the ionic character of such solids shifts towards atomic bonds at elevated temperatures (68) at which reactions take place. The formation of atoms or atom-molecules is at any rate favored at surfaces and other lattice disturbances in ionic lattices because of the asymmetry of charges there (*cf.* 9). Figure 13 illustrates the trend towards molecule formation at a surface of barium oxide. According to a hypothesis by Hedvall (53) a state of anomalous polarization which may be produced locally in the interior by thermal fluctuations of the lattice vibrations may be transmitted from neighbor to neighbor until it reaches an internal or external surface at which it materializes as a reactive surface molecule.

In some reactions it has been shown experimentally that the migrating particles consist of entire groups. It was found early that the reaction $MgO + ZnWO_4 \rightarrow ZnO + MgWO_4$ appeared to proceed by migration of WO_3 groups (87). Recently, careful experiments by Jagitsch have shown that the reactions:

$$PbO + PbSiO_3 \rightarrow Pb_2SiO_4 \quad (82)$$

$$2PbO + Pb_2SiO_4 \rightarrow Pb_4SiO_6 \quad (82)$$

$$MgO + Mg_2P_2O_7 \rightarrow Mg_3(PO_4)_2 \quad (84)$$

are performed by migration of PbO and P_2O_5, respectively. At the present time this migration of uncharged particles is only sketchily understood.

Since lattice imperfections can always be present in newly formed phases, the concentration of mobile particles in the reaction products may be greater than required thermodynamically, and high reaction rates are therefore to be expected. This was actually the case in several systems investigated by Wagner (162), in which the observed rates were several times larger than the calculated ones. It is indeed rather surprising that the kinetics of some reacting systems are controlled by the thermodynamic disorder. This is possible because most of the reaction products in these systems possess a completely disordered cation lattice. Since the degree of thermodynamic cation disorder is 100 per cent, no appreciable contribution of additional lattice imperfections to the reaction rate is observed. The bulk of reactions in the solid state, however, has to be characterized empirically.

B. Characterization of lattice imperfections

In order to gain an insight into the reaction possibilities of a solid it is desirable to ascertain in as great detail as possible the particular states in which the solid can be obtained. The characterization is empirical and is obtained by combining the results of measurements of various properties of the substance in question. Some properties frequently investigated for this purpose are the following:

(1) The structural or textural state

(*a*) *Lattice expansion:* Occasionally a solid may occur with an anomalously expanded lattice instead of with normal dimensions. This is illustrated in table 6 on tricalcium silicate prepared by the solid-phase reaction (89): $CaCO_3 + Ca_2SiO_4 \rightarrow Ca_3SiO_5 + CO_2$. The stretching of the lattice is evident by comparing the angles of reflection of powder photographs with those of the normal compound.

(*b*) *Average particle displacement and partially amorphous state:* More frequently occurring than the stretching of the entire lattice are irregular dislocations of lattice particles without change of the over-all parameters. Part of the compound may even be present in the form of x-ray amorphous aggregates. In table 7 these conditions are shown for ZnO and α-Fe_2O_3 prepared by dehydration of their hydroxides (33, 34, 36). The average distortion is greatest at the lowest temperature of preparation; at higher temperatures, the thermal motion causes the lattice particles to approach their normal positions. The crystallites grow, whilst the lattice distortion and the content of amorphous compound diminish.

TABLE 6

Expanded lattice of fresh reaction product

STATE OF Ca_3SiO_5	REFLECTION ANGLES OF POWDER PHOTOGRAPHS						
Normal lattice	15.10	16.50	17.50	21.00	26.30	28.50	31.60
Freshly formed lattice	14.90	16.40	17.40	20.90	26.10	28.40	31.40

TABLE 7

Effect of thermal treatment on lattice imperfections

HEAT TREATMENT			AVERAGE SIZE OF GRAIN (ZnO) OR CRYSTALLITE (Fe_2O_3)		AVERAGE PARTICLE DISPLACEMENT	FRACTION OF AMORPHOUS SUBSTANCE	MOLAR HEAT OF SOLUTION CORRECTED FOR WATER CONTENT
Temperature	Time	Water content					
°C.	*hours*	*per cent*	Å.		Å.	*per cent*	*kg.-cal.*
Vacuum heated			ZnO				
100	13	3.07	8,000		0.12	10–20	23.6
82	33	3.14	4–8,000		0.11	10–20	23.0
300	5	0.66	8–12,000		0.08	0	22.45
Heated in N_2							
600	6	0.03	8–16,000		0	0	22.3
			α-Fe_2O_3				
Vacuum heated			Hexagonal axes				
			a	*c*			
240	1	1.68	181	100	0.21	0	54.0
Heated in air							
300	1	1.45	191	103	0.18	0	51.5
410	1	0.89	191	151	0.11	0	50.7
600	1	0.36	204	180	0	0	49.3

(*c*) *True and apparent density, grain size, porosity, and specific surface:* The degree of dispersion, the surface development, and the details of the surface structure can be ascertained by numerous direct or indirect methods which have been thoroughly discussed in recent reviews (*cf.* 1, 42, 168), and to these, therefore, no further space is devoted in this article. An interesting method may be noted, introduced by O. Hahn (40, 41), in which a radioactive tracer is incorporated within the solid generating emanation. From measurements of the amount of emanation escaping from the solid, valuable information on the textural state may be obtained (30, 80, 81, 167).

2. The energy state

(*a*) *Energy content:* The excess energy content caused by the occurrence of non-equilibrium imperfections or by a large surface development has been determined from measurements of the heat of solution. Examples of such measurements are included in table 7. In the case of α-Fe_2O_3 specimens with an excess energy up to 10 per cent of the normal value are reported, an excess which may influence the reactivity tremendously.

(*b*) *Magnetic susceptibility:* In general the different lattice states of a substance do not appear to alter the magnetic susceptibility, in particular not that of diamagnetic substances (169). In some instances, however, a dependence of the susceptibility on lattice imperfections has been reported (*cf.* 131); for instance, ZnO prepared by decomposition of the oxalate showed after heating for 6 hr. at 300°C. a susceptibility of -0.29×10^{-6}, whereas after heating for 6 hr. at 550°C. the susceptibility was -0.43×10^{-6} (76).

A distinct correlation between the magnetic state and catalytic surface activity has been observed with ferromagnetic substances (58, 59). In at least one case it was established that both the activation energy and the pre-exponential factor in the Arrhenius equation of the reaction rate constant are greater in the paramagnetic state than in the ferromagnetic state (16).

(*c*) *Surface activity:* It is well known that the surface activity of a solid, as expressed by sorptive and catalytic action, varies with different states of a compound and may, therefore, be employed for a characterization. Considerable work from this standpoint has been carried out and has recently been surveyed by Fricke (32) and by Hüttig (75).

The dependence of the surface activity on the energy state of the lattice is further indicated by observations of the discontinuous change of the rate of dissolution of seignette salt at the electrical Curie point (65), and of the change in the adsorption equilibrium of phenolphthalein on cadmium sulfide upon irradiation (55).

C. Significance of lattice state for reactivity

The increase in chemical potential due to structural or textural disturbances exerts an accelerating influence on reactions of solids which may be illustrated by a few examples.

The difference in reactivity of a compound when it is rich in internal defects or when it is in a comparatively perfect state is brought out by figure 14, which refers to the reaction between calcium oxide and ferric oxide (66). Two different types of ferric oxide were prepared by decomposition of ferric sulfate and ferric oxalate, the former being heavily defective. Despite its greater grain size, the "sulfate" oxide reacts much faster with calcium oxide than does the "oxalate" oxide. At higher temperatures the differences in activity are eliminated.

An instance of differential activity produced by special pretreatment of one of the reacting components is found in the formation of calcium silicate from calcium oxide and silica (figure 15) (54). The silica had been preheated in the presence of gases which cannot interact chemically with silica in the usual sense, such as oxygen, sulfur dioxide, and sulfur trioxide, but which nevertheless affect the lattice state by penetration or dissolution. Quartz preheated in sulfur trioxide was least active; heating in air increased the reactivity and still more did heating in oxygen or sulfur dioxide.

A reacting component has a greater reactivity when it is formed in contact with its partner. This is shown by figure 16 for the formation of magnesium chromite from ferrous chromite and magnesia or magnesium carbonate (64). Magnesium carbonate decomposes at the temperatures of the reaction and is more reactive than is magnesium oxide.

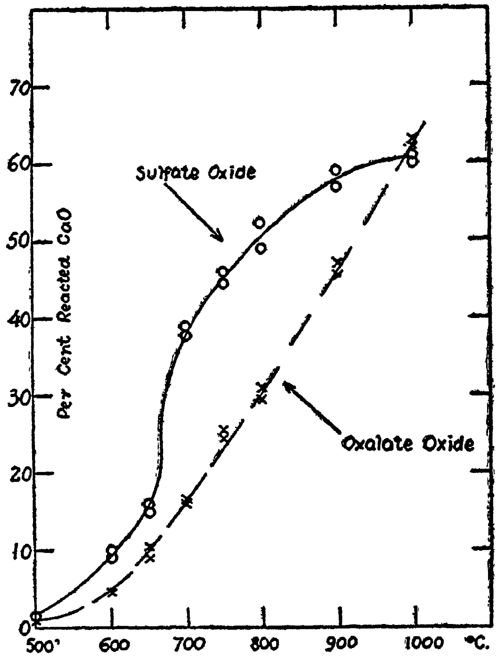

FIG. 14. Significance of parent substance on reactivity of ferric oxide (Hedvall and Sandberg (66)).

An especially active state exists during the course of a crystallographic transformation, because the bonds between lattice particles are weakened or even broken during the transition. While the transition proceeds, the crystal has a maximum activity in reactions with surrounding phases (Hedvall's rule). Figure 17 shows the relative rate maximum for the reaction between barium oxide and silver iodide, yielding barium iodide and silver oxide at the transition point of silver iodide (145°C.) (57). This relative rate maximum is, of course, observed only when the time of reaction is of the same order of magnitude as the time within which the transition occurs. Correspondingly, the "reaction temperatures" of exchange reactions involving oxygen-containing acid groups, which were found constant and independent of the nature of the salt-component (*cf.* table 2), are lowered to approximately the transformation temperature provided this temperature lies below the normal reaction temperature of the basic oxide. Examples are given in table 8 (60c).

D. Qualitative picture of reaction mechanism

By means of such criteria, an interpretation of the various stages of a reaction between solids may be arrived at. However, unless a general validity can be proved experimentally, the mechanism observed and the nature of the products formed apply only to the specific reaction conditions and may vary with the state of the reactants, composition of the reaction mixture, reaction temperature and time, and with other conditions.

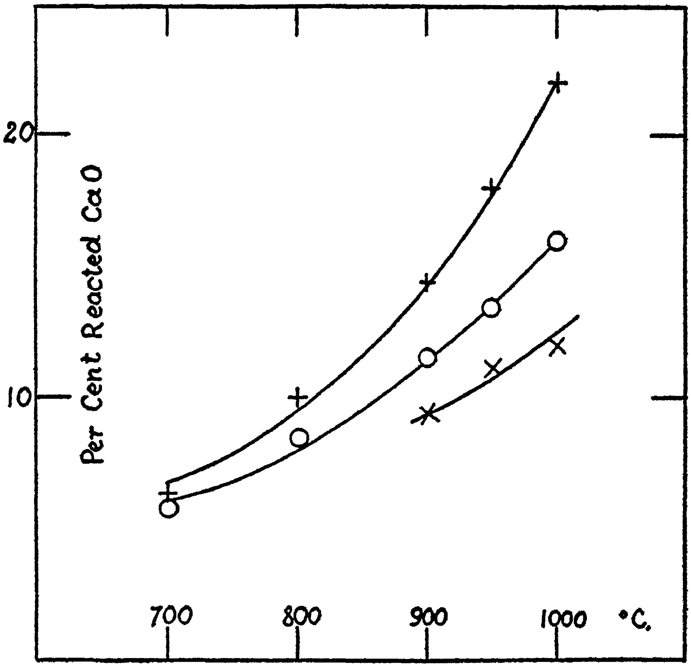

FIG. 15. Dependence of reactivity of silica on pretreatment (Hedvall *et al.* (54))

Figure 18 shows the sequence of compound formation with an equimolar mixture of silica and calcium oxide at 1200°C. (94). In this mixture the metasilicate is the only stable product; nevertheless the orthosilicate and tricalcium disilicate are formed first and become gradually converted into the metasilicate.

The dependence of the nature of the product on the composition of the reaction mixture and on the reaction temperature under conditions otherwise identical is illustrated by figure 19, which exhibits the reaction between barium carbonate and ferric oxide (25). In this system the following products have so far been identified: $BaO \cdot 2Fe_2O_3$; $BaO \cdot 6Fe_2O_3$; $Ba_8Fe_8O_{21}$. The regions of existence for the last two compounds are given by the contour lines of figure 19, the numbers of the contour lines indicating the relative proportions to which the compounds were formed under the existing conditions.

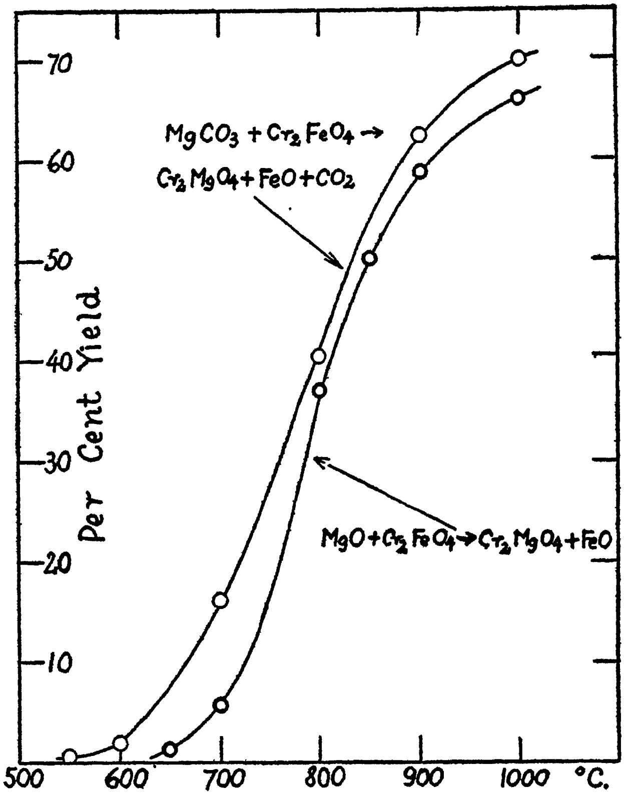

Fig. 16. Increased reactivity of nascent reactant (Hedvall and Ny (64))

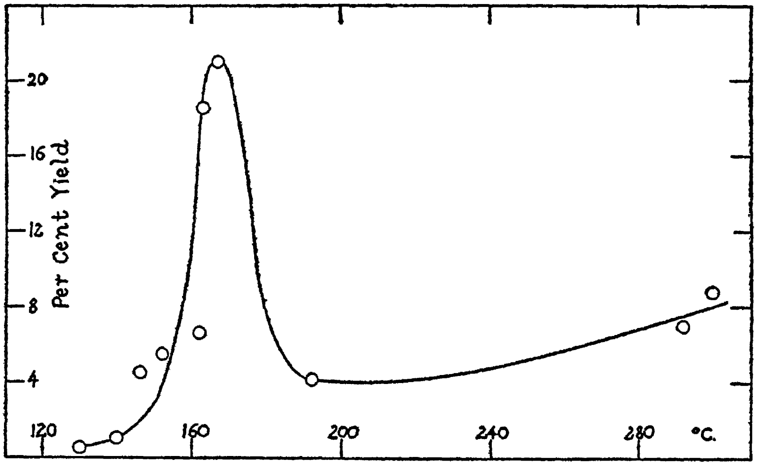

Fig. 17. Relative reactivity maximum of silver iodide at crystallographic transition point (Hedvall *et al.* (57)).

With other systems, however, it was found that, under all conditions studied, a given primary product was formed which subsequently may have been converted into more stable compounds, depending on the composition of the reaction mixture and on the temperature. In table 9 are listed the primary products for a number of reactions as compiled by Jander (88). This behavior can be utilized for the preparation of pure compounds by solid-phase reaction from the appropriate reaction mixture, which might not be possible of preparation by fusion.

TABLE 8

Induction of reaction by crystallographic transition

BASIC OXIDE	REACTANT			
	$AgNO_3$		Ag_2SO_4	
	Transition	Reaction	Transition	Reaction
	°C.	°C.	°C.	°C.
BaO		170		342
SrO	160	172	411	422
CaO		164		422

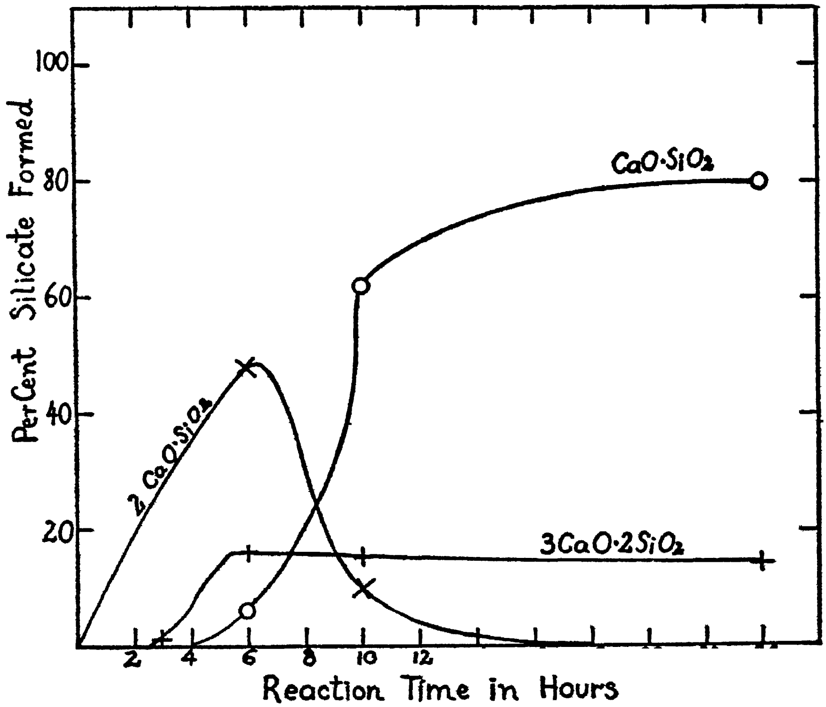

FIG. 18. Sequence of compound formation in system CaO + SiO_2 (Jander and Hoffmann (94)).

The preferred initial formation of a given compound appears to depend on the relation of the diffusion rate to the rate of nucleation. For instance, it was found that in equimolar mixtures of calcium oxide and silica the orthosilicate stage was passed more quickly the finer the grain size of the powder mixture (70), and in equimolar mixtures of magnesium oxide and silica the orthosilicate stage was completely omitted when the mixture was prepared in "molecular dispersion" by precipitation (146).

In simple additive reactions yielding only one product (A + B → AB), a certain pattern for the various stages of the reaction has been brought out by numerous investigations which seems to hold in principle either for different temperatures and constant reaction times or for constant temperature and different times. As illustration of this pattern, the formation of zinc iron spinel from zinc oxide and ferric oxide may be described. Powder mixtures of zinc oxide and iron oxide were kept for given times at given temperatures, and the changes in certain physical and chemical properties were determined. Some of these measurements are shown in figure 20, in which are plotted the densities of the reacting system (77), the catalytic action on the oxidation of carbon monoxide by oxygen at 250°C. (78), the intensity of one characteristic powder diffraction line for each component (93), the average particle displacement in the freshly formed spinel lattice, and the molar heat of solution (35). At each temperature of observation, a certain step in the reaction has occurred. The intermediate stages are pictured schematically in figure 21, and the same sequence of steps may be expected to take place at other temperatures and times.

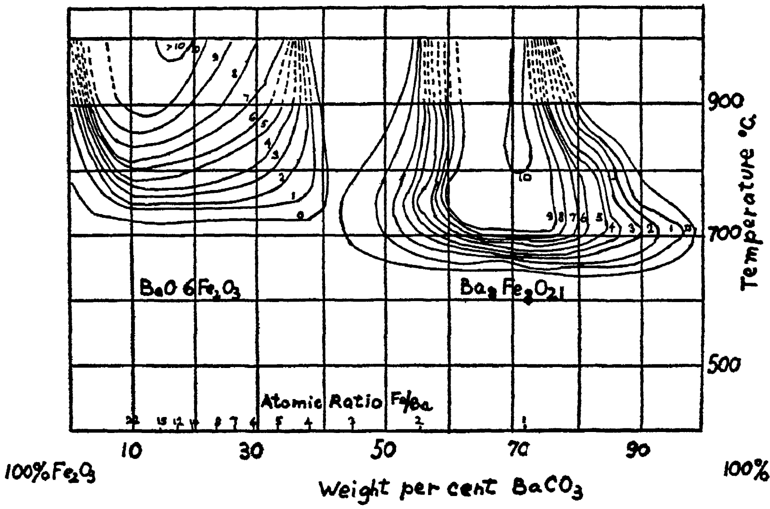

FIG. 19. Formation of BaO·6Fe_2O_3 and $Ba_8Fe_8O_{21}$ in system $BaCO_3$ + Fe_2O_3 (Erchak, Fankuchen, and Ward (26)).

(*1*) *Period of primary interaction:* Even upon mixing the reactants (designated in the following as A and B) at ordinary temperature, an interaction is observed unless the substances have been thoroughly aged. This interaction may appreciably increase the number of adsorbing centers at the surface. Figure 22 shows that the adsorption of lead nitrate is increased about sixfold upon mixing the oxides (138). The increase in adsorptive power is apparently connected with the chemical affinity between zinc oxide and ferric oxide; it is not observed, for instance, in mixtures of ferric oxide and chromic oxide.

Slight heating of the reaction mixture, however, causes the surfaces of the reactants to become more closely attached to each other, with the result that the specific surface, as determined by the amount of organic dyes adsorbed, decreases, and the density increases.

TABLE 9

Primary products of reactions in the solid state

REACTING SYSTEM	COMPOUNDS FORMED BY SOLIDIFICATION OF MELTS (MOLAR RATIO)	PRIMARY COMPOUND FORMED BY REACTION IN SOLID STATE
$MgO–Al_2O_3$	1:1	$MgO \cdot Al_2O_3$
$CaO–Al_2O_3$	3:1; 5:3; 1:1; 3:5	$CaO \cdot Al_2O_3$
$BaO–Al_2O_3$	3:1; 2:1; 1:1	$BaO \cdot Al_2O_3$
$CaO–Fe_2O_3$	2:1; 1:1	$CaO \cdot Fe_2O_3$
$MgO–TiO_2$	2:1; 1:1; 1:2*	$MgO \cdot TiO_2$*
$MgO–SiO_2$	2:1; 1:1	$2MgO \cdot SiO_2$
$CaO–SiO_2$	3:1; 2:1; 3:2; 1:1	$2CaO \cdot SiO_2$
$SrO–SiO_2$	2:1; 1:1	$2SrO \cdot SiO_2$
$BaO–SiO_2$	2:1; 1:1; 2:3; 1:2	$2BaO \cdot SiO_2$
$PbO–MoO_3$	2:1; 1:1	$PbO \cdot MoO_3$
$PbO–WO_3$	2:1; 1:1	$PbO \cdot WO_3$
$CaO–MoO_3$ $CaO–WO_3$ $BaO–MoO_3$ $BaO–WO_3$	Constitution diagram incompletely known; identified 1:1	$CaO \cdot MoO_3$ $CaO \cdot WO_3$ $BaO \cdot MoO_3$ $BaO \cdot WO_3$
$MeO–UO_3$ (Me = Mg, Ca, Sr, Ba, Zn, Cd, Hg, Pb, Ni)	Constitution diagram incompletely known; identified 1:1; 1:2	$MeO \cdot UO_3$

* According to reference 91.

(2) *Formation of surface molecules (period of first activation):* At relatively low temperature, some surface particles of A or B become mobile enough to leave their original positions and to become attached to the surface of the other component. A surface molecule of AB is thus formed, without any diffusion into the other lattice and without the formation of the normal AB structure. The surface film so formed is not coherent and is loosely bound. In this stage the reaction mixture shows a relative maximum of the catalytic action. There is apparently not only a maximum yield of the catalytic reaction, but also a maximum of the number of active centers on the catalyst surface. This phe-

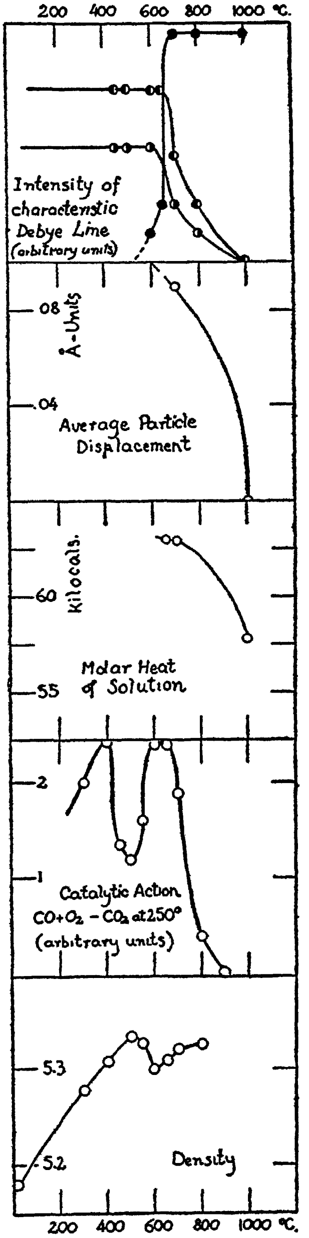

FIG. 20. Properties of reaction system ZnO + Fe_2O_3

nomenon has been observed during the formation of zinc aluminum spinel from zinc oxide and alumina (90).

(3) Completion of molecular surface film (period of first deactivation): By increasing the reaction temperature somewhat more, a complete layer of AB

molecules is formed by surface diffusion of the mobile component. The film is relatively stable and the molecular forces between the AB molecules are

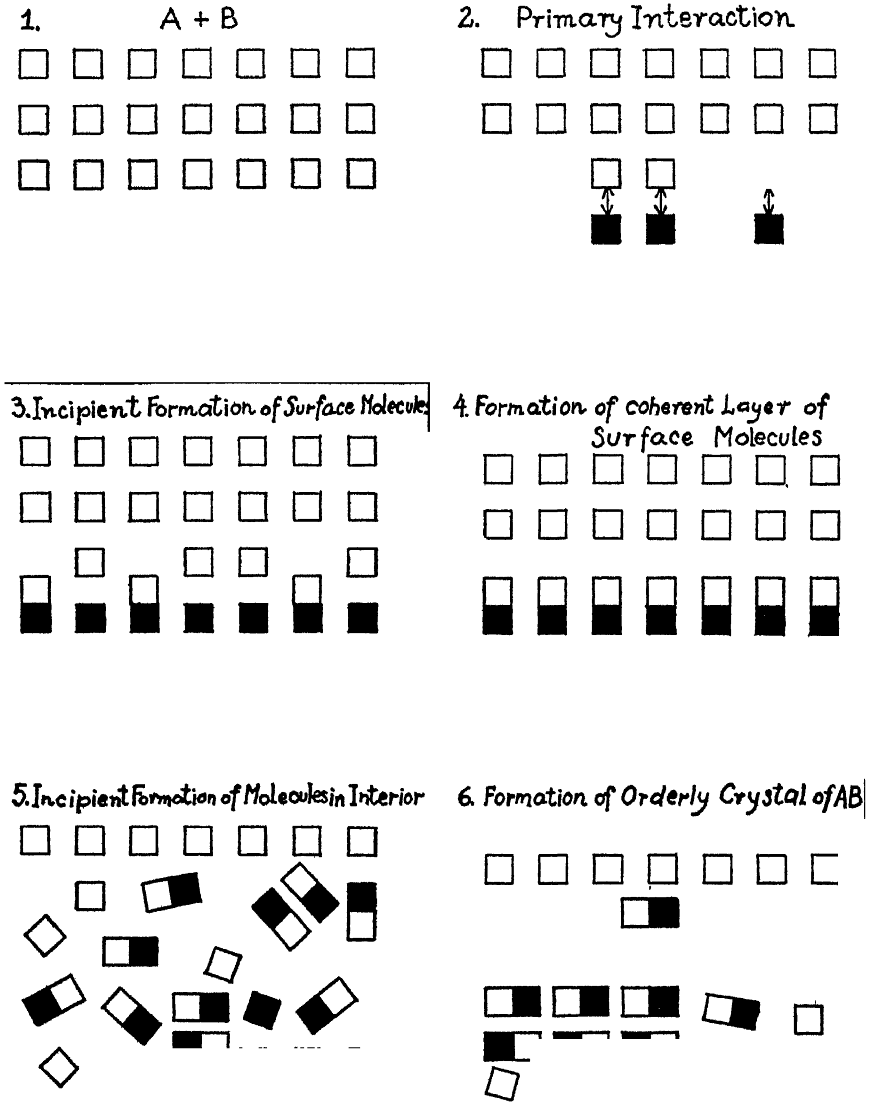
1. A + B
2. Primary Interaction
3. Incipient Formation of Surface Molecules
4. Formation of coherent Layer of Surface Molecules
5. Incipient Formation of Molecules in Interior
6. Formation of Orderly Crystal of AB

FIG. 21. Intermediate stages of spinel formation (ZnO + Fe_2O_3)

balanced. The catalytic activity, therefore, is markedly lower, while the density of the reaction mixture has increased further.

So far, the interaction between A and B has involved only a motion of surface particles possessing excess energy. These stages are, therefore, especially structure-sensitive, and the interaction between A and B is not detectable by chemical analysis or by x-ray measurements.

(*4*) *Formation of molecules of* AB *by diffusion into the interior* (*period of second activation*): At still higher temperatures particles may diffuse through the first layer of the reaction product into the interior of the other lattice. An unstoichiometric layer of AB in A or B is formed, the boundary of which moves gradually into A or B. Initially the reaction product is formed in a very imperfect state; the catalytic activity, therefore, is again at a maximum, whereas the diffuse state of the reaction product causes a minimum of the density. It is worth noting that in the zinc iron spinel formation the reaction product immediately shows the correct, though very imperfect, crystal structure. The initial, practically amorphous layer can be only a few molecules thick, since the diffraction lines of the spinel appear as soon as the intensities of the lines of zinc oxide and

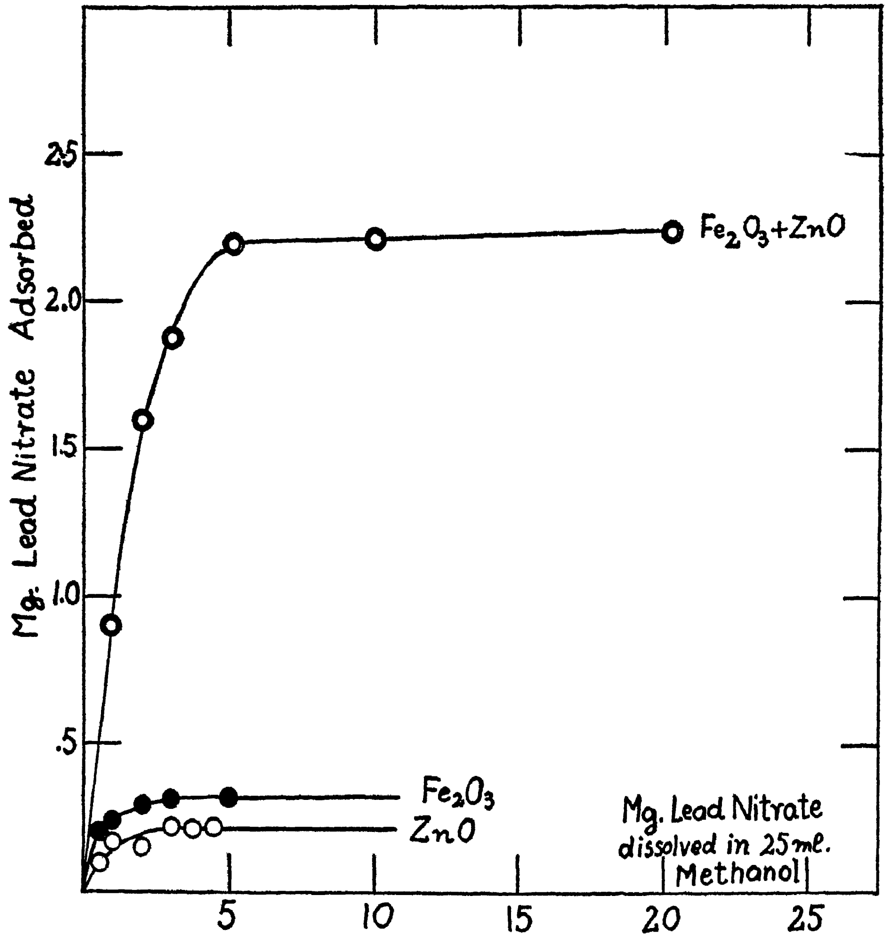

FIG. 22. Increased adsorption of mixture of ZnO and Fe_2O_3 (Starke (138))

iron oxide begin to decrease. In this stage, however, some extra lines were observed indicating a possible deviation from the normal spinel structure (93). The spinel lines were quite sharp from the beginning, indicating that the number of nuclei of the new phase must be very small (35). Initially, the size of the spinel crystals must be very small, and therefore the diffraction lines should have considerable breadth; however such lines are not observed, so the number of crystals must be small and can be detected only after a certain growth. In other cases, however, appreciable amounts of amorphous reaction product may be formed in this period if the crystallization is sluggish.

(*5*) *Formation of orderly crystallized* AB (*period of second deactivation*)*:* The freshly formed product has an imperfect lattice, as indicated by the average particle displacement and by the anomalously large heat of solution. The distorted state makes possible a relatively rapid diffusion through the layer of reaction product, that is, a relatively high reaction rate. With rising temperature the lattice imperfections disappear and increasing amounts of normal reaction products are formed; the catalytic activity, therefore, decreases and the density again increases. As the reaction product approaches perfection, the diffusion, i.e., the reaction rate, slows down. Nevertheless the reaction may be practically completed before the product has become free from all nonthermodynamic disorder, and no stage of the reaction may be governed by the thermodynamic disorder.

It should be emphasized that the picture just described is based on circumstantial evidence. Despite this limitation it seems possible for the present to reach a qualitative understanding of solid-phase reactions by charting the changes of a sufficient variety of properties of the reacting system, even when more than one reaction product is formed from the reacting components. An interesting beginning in this direction has recently been made by Ward and coworkers with the system $BaCO_3$–Fe_2O_3 (25, 26).

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COÖRDINATION COMPOUNDS OF BORON BROMIDE AND BORON IODIDE

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Boron bromide and boron iodide have been reported to form fewer coördination compounds than boron trichloride and boron trifluoride. A comparison of similar compounds formed by these halides indicates that the acceptor property of the boron atom in these halides is best with boron trifluoride and becomes systematically weaker to boron iodide. This is to be expected, inasmuch as the electronegativity of the halogen atoms becomes smaller from fluorine to iodine; consequently the boron atom becomes more electronegative by induction with an increase in the molecular weight of the boron halide.

Coördination compounds have been reported with boron bromide and molecules in which nitrogen, phosphorus, and arsenic atoms of Group V, oxygen and sulfur atoms of Group VI, and chlorine and bromine atoms of Group VII behave as donors.

Only compounds with ammonia have been reported to form coördination compounds with boron iodide, and the existence of these compounds has been questioned.

In earlier papers the coördination compounds of boron trifluoride (6, 18) and boron trichloride (19) have been reviewed. Owing to the interesting relationships existing between the compounds of these two boron halides, it is of interest to review critically the molecular compounds formed by the bromide and iodide of boron and to compare the properties of these compounds with analogous compounds of the chloride or fluoride. These compounds will be discussed according to the group in the Periodic Table of which the donor atom is a member.

As was expected, and as was found to be the case with boron trifluoride and trichloride, no molecular compounds involving boron bromide or boron iodide have been reported in which the donor atom is a member of Group I, II, or III of the Periodic Table. With boron trifluoride it was postulated that the carbon atom was a donor to form an unstable, intermediate molecular compound with an organic molecule in condensation and polymerization reactions in which boron trifluoride is used as a catalyst (6, 18). However, no analogous compounds have been reported for the other halides of boron.

GROUP V

Nitrogen

It was reported as early as 1846 by Poggiale (23) that 1 volume of boron bromide reacts with 1.5 volumes of gaseous ammonia to produce a white, pulverulent solid which is somewhat volatile and has a sharp taste. This compound, $3NH_3 \cdot 2BBr_3$, decomposes in water forming ammonium bromide and ammonium borate. The analogous compound with boron trichloride, $3NH_3 \cdot 2BCl_3$, had been reported much earlier by Berzelius (2) and confirmed somewhat later by Martius

(21). It is difficult to account satisfactorily for the distribution of the electrons required to establish the bonds in these compounds.

Besson (5) later studied the reaction of dry gaseous ammonia with boron bromide and reported that the reaction proceeds with the liberation of a large quantity of heat and the formation of some boron nitride. In order to obtain a definite compound Besson found it necessary to avoid a rise in temperature.

More recently, Pohland (24) studied the reaction of ammonia and boron bromide in the gas phase at a pressure of 5 mm. The reaction is exothermic and produces a white cloud of reaction product which contains 4.5 moles of ammonia per mole of boron bromide. This would correspond to the compound $9NH_3 \cdot 2BBr_3$. When the reaction product was heated in a vacuum to 300°C. ammonium bromide was found to be present.

Unfortunately the conditions were not adequately described by the earlier workers and therefore it is not possible to draw any definite conclusions with regard to the gas-phase reaction of ammonia with boron bromide except at reduced pressure. It is apparent however that the heat of reaction must be dissipated or the molecular compounds formed will decompose and, if the temperature is high enough, may be converted to boron nitride.

Joannis (16) allowed dry gaseous ammonia to react with precooled (−10°C.) liquid boron bromide. Under these conditions he reported that he obtained boron imide and ammonium bromide as products. At 0°C. Joannis observed that this reaction proceeded according to the equation:

$$2BBr_3 + 27NH_3 \rightarrow 6(NH_4Br \cdot 3NH_3) + B_2(NH)_3$$

The product $NH_4Br \cdot 3NH_3$ was identified by its vapor pressure, which was close to that reported by Troost (32). Upon warming to 20°C., $NH_4Br \cdot 3NH_3$ dissociates with the evolution of 9 moles of ammonia per mole of boron bromide, thus:

$$2BBr_3 + 27NH_3 \rightarrow 18NH_3 + 6NH_4Br + B_2(NH)_3$$

Several years later Stock and Holle (27) studied the reaction of gaseous ammonia with an excess of precooled, vigorously stirred boron bromide. Under these conditions, boron bromide was always occluded in the reaction product, which immediately underwent hydrolysis.

From the above work, it appears that gaseous ammonia reacts with liquid boron bromide to produce boron imide and ammonium bromide.

In order to dilute the reactants, Besson (5) studied the reaction of gaseous ammonia with a solution of boron bromide in carbon tetrachloride. By introducing precooled (0°C.) dry gaseous ammonia into the solution, also at 0°C., he obtained a white precipitate which was freed of the excess solvent by passing preheated (50–60°C.) dry air through the reaction vessel. The white amorphous product was found by analysis to have a composition in agreement with the formula $4NH_3 \cdot BBr_3$. This compound when heated in an atmosphere of dry hydrogen at 150°C. begins to decompose, without sublimation, to form boron nitride and ammonium bromide in accordance with the equation:

$$4NH_3 \cdot BBr_3 \rightarrow BN + 3NH_4Br$$

The obtainment of boron bromide by heating confirms the earlier observation of Besson that the heat evolved when the reactant gases are mixed produces boron nitride. Water and alkalies decompose $4NH_3 \cdot BBr_3$. At 10°C. the compound absorbs ammonia up to the ratio of 2 moles of compound per mole of ammonia, thus producing $9NH_3 \cdot 2BBr_3$ (*vide supra*). Besson, however, considered this absorption to be of a physical nature, although the resultant product is analogous to $9NH_3 \cdot 2BCl_3$, which he had reported earlier (3).

Stock (25) observed that the compound $AsH_3 \cdot BBr_3$ (*vide infra*) reacts with ammonia at 10°C. to produce $9NH_3 \cdot 2BBr_3$. It is to be noted that the temperature is the same as employed by Besson (5) and that the identical product is obtained. Stock observed that the combining ratio of ammonia to boron bromide varies inversely with the reaction temperature. At −25°C. for example, $9NH_3 \cdot 2BBr_3$ absorbs sufficient ammonia to become a liquid, which upon warming evolves the excess ammonia.

Joannis (15) studied the reaction of ammonia and boron chloride by allowing gaseous boron chloride diluted with hydrogen to react with liquid ammonia. He bubbled hydrogen through boron chloride at 0°C. and introduced the gases into liquid ammonia at −70°C. to −50°C. Under these conditions he obtained a white precipitate in the liquid ammonia. The excess ammonia was removed by allowing the reaction vessel to warm to −23°C. According to Joannis the reaction proceeds as indicated by the equation:

$$BCl_3 + 15NH_3 \rightarrow B(NH_2)_3 + 3(NH_4Cl \cdot 3NH_3)$$

Upon warming the product to 0°C., 9 moles of ammonia are liberated. The reaction between ammonia and boron chloride at 0°C. is represented therefore by the equation:

$$BCl_3 + 6NH_3 \rightarrow 3NH_4Cl + B(NH_2)_3$$

In view of this experimental work and that which he did with gaseous ammonia and liquid boron bromide, Joannis questioned the formation of $4NH_3 \cdot BBr_3$ and $9NH_3 \cdot 2BBr_3$ by the reactions reported above. He suggested that it was quite probable that the reaction products were mixtures of boron amide and ammonium bromide.

Stock and Holle (27) studied the reaction between liquid boron bromide and liquid ammonia. The boron bromide was allowed to drip into liquid ammonia with the formation of soluble ammonium bromide and insoluble boron amide. Upon heating the product to 750°C., ammonium bromide sublimed leaving boron nitride.

Apparently the reaction between ammonia and boron bromide is highly sensitive to the experimental conditions. At high dilution (for example, in the gas phase or when a diluent is used with the liquid boron bromide) and at lower temperatures the evidence favors the existence of molecular compounds. However, these compounds are seemingly very unstable to heat and are easily decomposed at moderate temperatures to form boron amide and ammonium bromide. At higher temperatures, boron nitride is formed. When the ammonia and boron bromide reactants are more concentrated (for example, liquid-phase reactions) apparently the reaction is so exothermic that any molecular compounds which might be formed at first are instantaneously decomposed to produce boron amide and ammonium bromide. These reaction products when heated similarly produce boron nitride.

It is quite clear that the reaction between ammonia and boron bromide proceeds vigorously and is exothermic and that the resultant molecular compounds are quite unstable. Their stability is seemingly less than that of the boron chloride compounds, which in turn are less stable than the compounds of ammonia and boron trifluoride.

The only molecular compounds of boron iodide reported in the literature are those with ammonia. Besson (5) observed that dry gaseous ammonia unites with boron iodide with the evolution of a considerable quantity of heat. As he observed with the analogous reaction with boron bromide above, a rise in temperature favors the formation of boron nitride. Precooled (0°C.) ammonia when introduced into a solution of boron iodide in carbon tetrachloride at 0°C. yields a white precipitate immediately upon the surface of the solution. Removal of the carbon tetrachloride by a current of warm dry air (50–60°C.) leaves an amorphous white solid, which was found upon analysis to have a composition corresponding to the formula $5NH_3 \cdot BI_3$.

This compound is unstable in the presence of light, slowly turning to a yellow color with the liberation of a small quantity of iodine. Iodine is produced also when the compound is heated in a current of hydrogen. The compound is quickly decomposed by water. A current of dry gaseous ammonia at 0°C. converts $5NH_3 \cdot BI_3$ into a pasty mass which eventually completely liquefies. Besson reported the composition of this product to be $15NH_3 \cdot BI_3$. At 0°C. this product is unstable and gradually evolves ammonia when maintained in a current of dry air to reproduce the compound $5NH_3 \cdot BI_3$.

Later, Joannis (15) stated that he believed the reactions of ammonia with boron iodide were of the same nature as those which he had observed for ammonia and boron chloride and that the above products were actually mixtures of boron amide and ammonium iodide. As pointed out above, the concentration of the reactants and the reaction temperatures employed alter these reactions and it could well be that the reaction under certain conditions would proceed in either of the ways reported by Joannis or Besson.

Table 1 summarizes the molecular compounds reported to be formed by ammonia with the boron halides.

Inasmuch as the boron atom becomes more positive as the molecular weight of the boron halide decreases, and inasmuch as the size of the molecule becomes smaller, it would be expected that the ratio of ammonia to boron halides in the molecular compounds should increase as the molecular weight of the boron halide decreases. As a consequence of the increased positive charge on the boron, more ammonia molecules should associate owing to an induced positive

TABLE 11

Molecular compounds of ammonia and the boron halides

Ratio of NH_3/BX_3....	1	1.5	2	3	4	4.5	5	15
BF_3.	$NH_3\cdot BF_3$		$2NH_3\cdot BF_3$	$3NH_3\cdot BF_3$				
BCl_3		$3NH_3\cdot 2BCl_3$				$9NH_3\cdot 2BCl_3$		
BBr_3............		$3NH_3\cdot 2BBr_3$			$4NH_3\cdot BBr_3$	$9NH_3\cdot 2BBr_3$		
BI_3							$5NH_3\cdot BI_3$	$15NH_3\cdot BI_3$

charge on the hydrogen atoms of the ammonia coördinating with the boron. This association should be favored also because steric hindrance is less likely to be encountered with the smaller halogen atoms. The reverse seems to be the case, as shown in table 1, and this along with the great instability reported for the compounds of the heavier boron halides seems to favor the postulates of Joannis that boron amide and ammonium halide are the products obtained in these cases. It is strange that more analogous compounds have not been reported for the boron halides with ammonia.

Johnson (17) studied the reactions of boron bromide with substituted ammonia compounds. He slowly passed methylamine and ethylamine, respectively, into a solution of boron bromide in carbon tetrachloride. By so doing he avoided any appreciable rise in temperature and obtained amorphous white products which upon analysis were found to have compositions in agreement with the formulas $(CH_3NH)_2BBr$ and $C_2H_5NHBBr_2$.

Using isoamylamine and aniline, he modified his technique by making a solution of the amine in carbon tetrachloride and adding a solution of boron bromide in carbon tetrachloride to the former. By cooling the reaction vessel with ice a violent reaction was avoided, although considerable heat was generated. By very slow addition of the solution of boron bromide, yellow to orange precipitates were formed at first, but after 1 mole of boron bromide had been added, amorphous white precipitates were obtained. These precipitates upon analysis were found to have compositions which may be represented by the formulas $i\text{-}C_5H_{11}NH_2 \cdot BBr_3$ and $C_6H_5NH_2 \cdot BBr_3$ (17).

Isoamylamine–boron bromide does not dissociate very rapidly below 40°C., turns a light yellow color in the sunlight, and is hydrolyzed energetically, especially by an alkaline solution, e.g., sodium hydroxide. When warmed rapidly, the compound appears to melt with immediate decomposition. It will ignite and burn vigorously with a green colored flame.

Aniline–boron bromide fumes strongly in air and is rapidly hydrolyzed to produce boric acid and aniline hydrobromide. Hydrolysis in an alkaline solution yields aniline oil.

On the basis of his work, Johnson (17) concluded that the lower primary amines tend to allow more than one molecule of the amine to react with one molecule of boron bromide to split out hydrogen bromide with the resultant formation of a heterogeneous imide. With five or more carbon atoms, the primary amines tend to form molecular compounds. This statement seems unproven, inasmuch as reactions with propyl- and butyl-amines are not reported to have been studied.

Using the same technique, Johnson (17) found that secondary amines react in a manner somewhat similar to the primary amines. The lone hydrogen atom of the aliphatic secondary amines (dimethyl-, dipropyl-, and diamyl-amines) readily splits out to form hydrogen bromide, giving rise to the stable products $(CH_3)_2NBBr_2$, $(C_3H_7)_2NBBr_2$, and $(C_5H_{11})_2NBBr_2$.

Piperidine and diphenylamine, however, form molecular compounds with boron bromide. Using carbon tetrachloride as a mutual solvent, piperidine and boron bromide were allowed to react to produce a very light yellow precipitate.

The precipitate was washed with carbon tetrachloride and dried in a current of either dry air or dry hydrogen. The product upon analysis was found to have a composition most simply expressed as $3(C_5H_{10}NH) \cdot BBr_3$. The product is unstable under ordinary conditions and is transformed into a stable product with the evolution of hydrogen bromide. The stable product is best obtained by exposing a thin layer of $3(C_5H_{10}NH) \cdot BBr_3$ to the action of calcium chloride and sodium hydroxide in a desiccator. The stable product was found by analysis to have a composition in agreement with the formula $2(C_5H_{10}NH) \cdot C_5H_{10}NBBr_2$. This substance dissolves in several organic solvents, apparently without decomposition, to produce greenish-yellow solutions possessing fluorescing properties.

Using a similar procedure, diphenylamine reacted with boron bromide to yield a voluminous, snow-white product which is more stable under ordinary conditions than the other secondary amine compounds. The formula of this compound was found by analysis to be $3(C_6H_5)_2HN \cdot BBr_3$.

It seems odd that 3 moles of these secondary amines can easily coördinate with 1 mole of boron bromide. Evidently these secondary amines associate, although the fact that there are three moles of amine and three bromine atoms might suggest hydrogen bonding. However, with bromine at these temperatures, this does not seem probable.

In this study of the reactions of tertiary amines with boron bromide, Johnson (17) found that a simple molecular compound usually forms at first, which later decomposes by splitting out an alkyl bromide. A stable molecular compound forms with quinoline, whereas with alkyl or mixed alkyl phenyl amines, less stable coördination compounds are formed. The conclusion follows that the size of the aromatic nucleus attached to the nitrogen atom and the stability of the resulting molecular compound are related.

When gaseous trimethylamine was introduced into a solution of boron bromide in carbon tetrachloride, an exothermic reaction occurred immediately with the formation of a small quantity of precipitate. Copious white fumes were evolved from the reaction liquid, and it was apparent that a general decomposition was occurring, perhaps with solution of the initial product. Attempts made to crystallize the product as a definite compound were unsuccessful.

With carbon tetrachloride as a common solvent, triethylamine and boron bromide were allowed to react. Heat was liberated and a white precipitate formed at first which later dissolved in the warm carbon tetrachloride. Fine, long, slender prisms which readily formed large irregular translucent masses were deposited upon cooling the solution. By permitting the carbon tetrachloride solution to stand for a period of time, bunches of "cotton batting-like" crystals formed and floated about in the solvent. These crystals were exceedingly thin long needles, having a length at least two hundred times their diameter. They were found to be relatively unstable when washed and dried, particularly at temperatures above 50°C. After being analyzed, the crystals were assigned the formula $(C_2H_5)_3N \cdot BBr_3$. The crystals readily, but not violently, underwent hydrolysis in water.

Boron bromide evidently does not react with triethanolamine, inasmuch as it was found that a solution of boron bromide in triethanolamine did not react with magnesium after being heated with it in a sealed tube at 120°C. for 3 hr. (9).

Dimethylaniline reacts rapidly with boron bromide, forming masses of small, translucent crystals which are somewhat soluble in carbon tetrachloride (17). The reaction is exothermic. To prevent hydrolysis, dry air must be used to dry the crystals. The hydrolysis with cold water is rapid but not violent and produces an oil, a white insoluble substance, and a small quantity of gas. According to the analysis, the product is dimethylaniline–boron bromide, $C_6H_5N(CH_3)_2 \cdot BBr_3$. When stored over sodium hydroxide and calcium chloride in a desiccator placed near a steam radiator, this compound evolved methyl bromide, leaving $C_6H_5NCH_3BBr_2$.

Pyridine, an example of a strongly basic organic compound of the heterocyclic nitrogen–carbon type, reacts with boron bromide in a carbon tetrachloride medium to produce a light, amorphous, snow-white precipitate (17). After the carbon tetrachloride has been removed, the product may be handled in air for some time without appreciable decomposition. Upon heating, the dissociation pressure rises rapidly with the temperature and at 120°C. the compound becomes "brown and crispy." By analysis the compound was found to be pyridine–boron bromide, $C_5H_5N \cdot BBr_3$. If pyridine–boron bromide is stored over sodium hydroxide and calcium chloride, hydrogen bromide is evolved to yield a more stable powder, $C_5H_4NBBr_2$.

Similarly, quinoline and boron bromide react to form the white product $C_9H_7N \cdot BBr_3$ (17). Less heat is liberated in this reaction than in the one above with pyridine. This compound is more stable under ordinary conditions than $C_5H_5N \cdot BBr_3$. It is decomposed relatively slowly in a cold alkaline solution.

The compounds formed by amines with boron halides are compared in table 2.

Pohland (24) observed a vigorous reaction when boron bromide was condensed over hydrogen cyanide and the reactants were allowed to warm to room temperature. Under these conditions sufficient heat is evolved to cause the hydrogen cyanide to polymerize. However, if the reaction is carried out under a greatly reduced pressure, white, sharp, needle-shaped crystals are obtained having the composition $HCN \cdot BBr_3$. This result is obtained regardless of which reactant is present in excess. The crystals are volatile at room temperature and melt in a closed tube at 70°C. with decomposition. The compound is decomposed by moisture, evolving gases having odors resembling hydrogen bromide and hydrogen cyanide.

Johnson (17) allowed methyl cyanide to react with boron bromide dissolved in carbon tetrachloride in a cooled reaction vessel. A beautiful, flaky, snow-white product, which is slightly soluble in carbon tetrachloride and may be recrystallized therefrom, was obtained. The dried powder was found by analysis to be methyl cyanide–boron bromide, $CH_3CN \cdot BBr_3$. At low temperatures the compound is stable but at 30°C. it dissociates rapidly. It quickly decomposes in water.

In 1866 Gautier (11) reported that boron trichloride reacts very rapidly with

TABLE 2

Molecular compounds formed by amines with boron halides

BF_3	BCl_3	BBr_3	BI_3
$(CH_3)_3N \cdot BF_3$	$(CH_3)_3N \cdot BCl_3$		None
$(C_2H_5)NH_2 \cdot BF_3$			
$(C_2H_5)_2NH \cdot BF_3$			
$(C_2H_5)_3N \cdot BF_3$	$(C_2H_5)_3N \cdot BCl_3$	$(C_2H_5)_3N \cdot BBr_3$	
$2(C_2H_5)_3N \cdot BF_3$			
		$i\text{-}C_5H_{11}NH_2 \cdot BBr_3$	
$(CH_2)_6N_4 \cdot 4BF_3$			
$C_{23}H_{26}N_2O_4 \cdot 4H_2O \cdot 2BF_3$			
$CH_3CONH_2 \cdot BF_3$			
$C_6H_5NH_2 \cdot BF_3$	$C_6H_5NH_2 \cdot BCl_3$	$C_6H_5NH_2 \cdot BBr_3$	
$C_6H_5N(CH_3)_2 \cdot BF_3$	$C_6H_5N(CH_3)_2 \cdot BCl_3$	$C_6H_5N(CH_3)_2 \cdot BBr_3$	
$p\text{-}CH_3C_6H_4NH_2 \cdot BF_3$(?)	$p\text{-}CH_3C_6H_4NH_2 \cdot BCl_3$		
$C_6H_5(CH_3CO)NH \cdot BF_3$			
$C_6H_5(CH_3CO)NCH_3 \cdot BF_3$			
$C_6H_5NHNa \cdot BF_3$			
$C_6H_5NHK \cdot BF_3$			
		$3(C_6H_5)_2NH \cdot BBr_3$	
$C_6H_5CH{=}NC_6H_5 \cdot BF_3$			
$C_6H_5C(NOH)CH_3 \cdot BF_3$			
$p\text{-}CH_3C_6H_4C(NOH)C_6H_5 \cdot BF_3$			
$C_5H_5N \cdot BF_3$		$C_5H_5N \cdot BBr_3$	
$C_5H_5N \cdot 2BF_3$			
$(CH_2)_5HN \cdot BF_3$		$3(CH_2)_5HN \cdot BBr_3$	
$C_9H_7N \cdot BF_3$		$C_9H_7N \cdot BBr_3$	

ethyl cyanide to produce a white crystalline compound which was found by analysis to have the formula $C_2H_5CN \cdot BCl_3$. The crystals are prisms which are perpendicular to a rhombic base. Upon heating, the crystals melt without appreciable decomposition, although they are quite volatile. Owing to decomposition a small portion of residue remains. When strongly heated, the crystals evolve acidic vapors smelling like cyanogen. The compound undergoes hydrolysis with the formation of hydrochloric acid, boric acid, and ethyl cyanide.

Gautier reported that a similar compound is obtained with boron bromide. Evidently the composition of this compound is $C_2H_5CN \cdot BBr_3$. Johnson (17) prepared this compound in the same manner in which he prepared methyl cyanide–boron bromide. He observed that the ethyl cyanide reacted with boron bromide with the evolution of more heat and that the product was more stable to heat and to hydrolysis than the methyl derivative.

Phenyl cyanide and boron bromide produce a substance which is quite soluble in carbon tetrachloride. With difficulty, Johnson (17) obtained good crystals which had a composition corresponding to the formula $C_6H_5CN \cdot BBr_3$. The pure white powder when dry is hygroscopic and hydrolyzes rapidly.

Comparatively little heat is evolved when boron bromide is allowed to react with benzyl cyanide. An amorphous, translucent mass results which forms clusters of needles around the edges. The dried product absorbs considerable carbon tetrachloride and is soluble to some extent in it. It is difficult to obtain well-formed crystals from the solution. Carbon disulfide was found to be a poorer solvent. Both solvents were used by Johnson (17) to obtain a final product which had a faint yellow color which is considered to be characteristic. The product fumes in air and melts with decomposition. The formula of the product was found by analysis to be $C_6H_5CH_2CN \cdot BBr_3$.

Silver cyanide and boron bromide have been reported to react at 60°C. to produce a yellowish-brown insoluble solid having a composition best expressed as $AgCN \cdot BBr_3$. The product is decomposed by water and ethanol to produce hydrogen bromide and hydrogen cyanide. Similar products are obtained when the crystals hydrolyze in moist air. Pohland (24) found that the product is black in color and is insoluble in the usual solvents when the reaction is carried out at 100°C. The molecular compound when heated to 150°C. evolved cyanogen, bromine, and boron bromide.

The fact that boron bromide, which is a poorer acceptor molecule than boron chloride, forms the above compound with silver cyanide is significant, because many years prior to this research Gustavson (13, 14) reported that neither silver cyanide nor potassium cyanide reacted with boron chloride to give boron cyanide. He did not give the conditions of his investigations, however.

Cocksedge (8) allowed boron bromide to react with twice the theoretical amount of dried silver thiocyanate in a benzene medium. He obtained a colorless solution which gave glistening colorless crystals upon the removal of the solvent at ordinary temperatures in a current of dry air. The crystals as usually obtained from benzene are short rhombic crystals, but occasionally they are obtained as radiating needles.

Analysis of the crystals indicated they were boron thiocyanate, $B(CNS)_3$. At 100°C. the crystals darken considerably. The product hydrolyzes to give boric and hydrothiocyanic acids. Later, Pohland (24) repeated the work of Cocksedge and was unable to confirm his preparation of boron thiocyanate. Instead, he obtained a light-stable, yellow product which could not be silver bromide, the by-product in the preparation of boron thiocyanate by the above reaction.

The reported cyanide compounds with the boron halides are tabulated in table 3. The pseudo-halogen group, CN, is apparently a better donor to boron halides than the chlorine atom. Methyl chloride was found by Booth and Martin (7, 18, 20) not to coördinate with either boron trifluoride or boron chloride, whereas methyl cyanide coördinates, as shown above.

TABLE 3

Molecular compounds of cyanides and the boron halides

BF_3	BCl_3	BBr_3	BI_3
$HCN \cdot BF_3$	$HCN \cdot BCl_3$(?)	$HCN \cdot BBr_3$	None
$CH_3CN \cdot BF_3$	$CH_3CN \cdot BCl_3$	$CH_3CN \cdot BBr_3$	
	$C_2H_5CN \cdot BCl_3$	$C_2H_5CN \cdot BBr_3$	
$C_6H_5CN \cdot BF_3$		$C_6H_5CN \cdot BBr_3$	
		$C_6H_5CH_2CN \cdot BBr_3$	
$CH_3C_6H_4CN \cdot BF_3$			
		$AgCN \cdot BBr_3$	

Phosphorus

Proceeding in Group VA to phosphorus it is interesting to note that the ammonia analog, phosphine, has been reported by Besson to form a one-to-one molecular compound with boron bromide (4). Being more electropositive, it is natural that the phosphorus atom would donate electrons more easily than the nitrogen atom and that the tendency for association with phosphine would be less than with ammonia. Hence we do not find compounds with more than one phosphine molecule per boron bromide molecule, as was the case with ammonia. On the other hand, as a consequence of association, the nitrogen atom of one of the associated molecules becomes sufficiently positive to coördinate, whereas the nitrogen atom in a single ammonia molecule is not sufficiently electropositive to coördinate. Hence, a one-to-one compound between ammonia and boron bromide has not been isolated.

Besson (4) observed that boron bromide absorbs phosphine at ordinary temperatures, producing a very light, white, amorphous solid which fumes in air and is spontaneously inflammable. When placed in water the product violently decomposes, evolving phosphine. It is reported that one may handle the compound in an atmosphere of carbon dioxide only with difficulty; consequently its analysis is difficult. The compound was found to have a composition best expressed as $PH_3 \cdot BBr_3$, as determined by the volume of phosphine which reacted with a known weight of boron bromide.

The dissociation pressure of the compound is negligible at ordinary temperature but is appreciable at 150°C. In a current of hydrogen or carbon dioxide in a closed system, the compound may be sublimed. The sublimate appears as small, transparent, very refractive crystals. When heated to 300°C. the compound first turns yellow, then brown, with the evolution of hydrogen bromide and the formation of phosphorus tribromide. Boron trichloride and boron trifluoride are reported to form the following compounds with phosphine: $PH_3 \cdot BCl_3$, $PH_3 \cdot BF_3$, and $PH_3 \cdot 2BF_3$.

About a year later, Besson (5) reported that boron iodide and phosphine react to yield a crystalline compound. He indicated that later he would publish the details of this research, but a search of the literature does not disclose this information.

Tarible (30) reported that boron bromide reacts instantly with phosphorus trichloride to produce a white crystalline compound. Considerable heat is evolved in this reaction. The reaction was carried out under various conditions, primary of which was the varying of the ratio of boron bromide to phosphorus trichloride from 0.5 to 3. The most lively reaction was obtained when 2 moles of boron bromide were allowed to react with 1 mole of phosphorus trichloride. When 3 moles of boron bromide were used, the excess liquid boron bromide appeared above the crystalline product and was decanted, leaving the crystals which were dried in a current of carbon dioxide. The analytical results corresponded with the formula $PCl_3 \cdot 2BBr_3$.

As would be expected, the colorless crystals fume in moist air and are completely hydrolyzed in water to yield phosphorous acid, boric acid, hydrogen bromide, and hydrogen chloride. The compound is soluble in its congeners, chloroform and carbon disulfide, but is insoluble in petroleum ether and vaseline oil. When heated, the compound partially sublimes at 40°C. and melts around 58°C. In a current of hydrogen the compound sublimes around 30°C. and is partially dissociated at 50°C. At red heat, oxygen reacts with $PCl_3 \cdot 2BBr_3$. Sulfur is unreactive with the compound below its dissociation temperature. Ammonia is absorbed by the compound in an exothermic reaction which yields a white crystalline product. Tarible found that hydrocarbons, ethers, alcohols, and organic acids react vigorously with the molecular compound.

Wiberg and Schuster (33) have studied the reaction of phosphorus trichloride and boron bromide more recently and were unable to confirm the above work of Tarible. The latter chemists allowed boron bromide and phosphorus trichloride to react in an apparatus maintaining a high vacuum and obtained a white crystalline product. The same product was obtained regardless of which reactant was present in excess. The excess reactant was distilled away from the product at −30°C. to prevent loss of the reaction product by sublimation. The reaction product was found to have a composition best expressed by the formula $PCl_3 \cdot BBr_3$.

The freshly prepared compound, $PCl_3 \cdot BBr_3$, melts at 42°C. and becomes a liquid when stored in a vacuum for several days. The crystals fume strongly in moist air and react vigorously with water producing a hissing noise and liberating considerable heat. The vapor pressure of the crystals was found to be 20 mm. at 18°C. and 21.5 mm. at 20°C.

Consideration of the bonds involved would surely favor the existence of $PCl_3 \cdot BBr_3$ over $PCl_3 \cdot 2BBr_3$.

The higher chloride, phosphorus pentachloride, does not react with boron bromide at ordinary temperatures, according to Tarible (30). However, if the reactants are placed in a sealed tube and heated to 150°C., yellow crystals, which are heavier than those of phosphorus pentachloride, are obtained. Tarible varied the molar ratios of the reactants in a manner similar to that described above for phosphorus trichloride. The compound upon analysis was found to have a composition in agreement with the formula $PCl_5 \cdot 2BBr_3$.

It is reported that the compound with the pentachloride is more stable than the analogous compound formed with the trichloride; this is probably due to the fact that the chlorine atom is the donor instead of the phosphorus atom. The pentachloride molecular compound is colorless, inasmuch as the pale yellow color obtained in the sealed tube disappears upon recrystallization from a solution of the crystals in boron bromide. Tarible attributed the color to traces of chlorine present in the phosphorus pentachloride. The compound is soluble in boron bromide and carbon disulfide but insoluble in petroleum ether and vaseline oil. Like the trichloride molecular compound, $PCl_5 \cdot 2BBr_3$ hydrolyzes in moist air and in water forming phosphoric and boric acids and evolving hydrogen bromide and chloride. The coördination compound is partially sublimed at 100°C. under atmospheric pressure and melts around 151°C. with slight decomposition. At elevated temperatures it sublimes in a current of hydrogen without decomposition. It is attacked by oxygen only at red heat. Below the dissociation temperature the compound is not attacked by sulfur, but ammonia is absorbed energetically and exothermally to produce a white amorphous powder. Hydrocarbons, ethers, alcohols, and organic acids react vigorously with the coordination compound.

Although the chlorine atom of phosphorus pentachloride is considered the donor atom in $PCl_5 \cdot 2BBr_3$, it was discussed at this point owing to its similarity to phosphorus trichloride.

Although oxygen is probably the donor in the compound formed by phosphoryl chloride and boron bromide, this compound will be discussed with the phosphorus chlorides. Oddo and Tealdi (22) allowed phosphoryl chloride and boron bromide to react and obtained a white crystalline product which was dried under reduced pressure on a clay plate supported over calcium oxide and sulfuric acid. Analysis of the crystalline product indicated the existence of the compound $POCl_3 \cdot BBr_3$. The compound hydrolyzes energetically and is easily decomposed, especially by potassium hydroxide. When heated, it decomposes prior to melting.

Tarible (29) found that phosphorus tribromide and phosphorus pentabromide form molecular compounds with boron bromide but unlike the phosphorus chlorides, the molar ratio is one to one. He observed that 1 mole of boron bromide when added to 1 mole of phosphorus tribromide produced a white crystalline compound which melted around 60°C. However, if carbon disulfide solutions of the two reactants were mixed and half of the solvent removed by distillation, the remaining solution produced either short thick crystals or needle-like crystals, depending upon the conditions of cooling. The crystals were freed from the solvent by a current of dry carbon dioxide and when analyzed were found to have the composition $PBr_3 \cdot BBr_3$. This crystalline product melted at 61°C.

As would be expected, the crystals fume in moist air and are very easily decomposed by water, producing boric and phosphorous acids and hydrogen bromide. The crystals are soluble in carbon disulfide and chloroform. When heated, they sublime with partial dissociation in a current of hydrogen. The compound is slightly decomposed by a current of oxygen at ordinary temperatures but ignites below red heat forming phosphoric oxide, boric oxide, and bromine. It was found that sulfur does not react with the crystals below their dissociation temperature. In a current of chlorine gas the compound is converted to $PCl_5 \cdot BCl_3$ by the displacement of bromine. Bromine, iodine, and other non-metals do not appear to react with the compound. Hydrogen chloride, hydrogen bromide, and hydrogen iodide do not react with the crystals but ammonia is absorbed exothermically to form a white crystalline compound. As reported for $PCl_3 \cdot 2BBr_3$, vigorous reactions are obtained with hydrocarbons, ethers, alcohols, and organic acids with $PBr_3 \cdot BBr_3$.

Tarible (29) observed that carbon disulfide solutions of boron bromide and phosphorus pentabromide produced a crystalline product when mixed. The reaction is exothermic. The product is not very soluble in cold carbon disulfide but is soluble when warmed. Small white crystals were obtained by recrystallization from carbon disulfide. The analysis of these crystals indicated that their composition was $PPr_5 \cdot BBr_3$.

The crystals turn yellow if placed in a sealed tube shortly after preparation. They fume in moist air and are decomposed energetically by water, forming phosphoric and boric acids along with hydrogen bromide. When heated in air the compound starts to volatilize at 105°C. The product melts at 140°C. in a sealed tube. A current of pure dry hydrogen does not react with the compound at ordinary temperatures, but upon heating the compound volatilizes and is entrained by the hydrogen. The crystals burn when heated to red heat in a current of oxygen. Chlorine displaces the bromine to produce $PCl_5 \cdot BCl_3$ exothermically. Ammonia reacts with $PBr_5 \cdot BBr_3$ with the evolution of heat to produce a white crystalline product.

This compound was discussed at this point owing to its similarity to the compound formed with PBr_3. However, in $PBr_5 \cdot BBr_3$ the donor atom is considered to be bromine.

Tarible (31) also studied the reaction of boron bromide with phosphorus diiodide. He allowed boron bromide to react with a carbon disulfide solution of phosphorus diiodide and obtained a yellow crystalline solid in a dark red liquid.

The product upon analysis was found to have a composition in agreement with the formula $P_2I_4 \cdot 2BBr_3$. The same product was obtained also by placing the reactants in a sealed tube.

$P_2I_4 \cdot 2BBr_3$ is a golden-yellow crystalline solid which rapidly hydrolyzes and decomposes in water to produce boric and phosphorous acids along with hydrogen bromide and hydrogen iodide.

The compound is soluble in boron bromide, carbon disulfide, and chloroform but insoluble in petroleum ether and vaseline oil.

When heated to 130°C. the compound evolves iodine and at 145°C. begins to fuse. When heated in a current of hydrogen the product sublimes without decomposition. In a current of oxygen it burns to yield boric oxide, phosphorus pentoxide, bromine, and iodine. With sulfur the compound yields an iodide of sulfur. Chlorine displaces the halogens to produce double chloride compounds. The composition of these was not given by Tarible, but if all the halogens are displaced $P_2Cl_4 \cdot 2BCl_3$ would result. However, it is questionable if P_2Cl_4 would form. $P_2I_4 \cdot 2BBr_3$ absorbs ammonia at elevated temperatures to produce a white amorphous powder.

TABLE 4

Molecular compounds of boron halides with halides of phosphorus

BF_3	BCl_3	BBr_3	BI_3
None	$PCl_3 \cdot BCl_3$	$PCl_3 \cdot BBr_3$	None
		$PCl_3 \cdot 2BBr_3$(?)	
	$PCl_5 \cdot BCl_3$	$PCl_5 \cdot 2BBr_3$	
	$P_2Cl_4 \cdot 2BCl_3$(?)		
		$POCl_3 \cdot BBr_3$	
		$PBr_3 \cdot BBr_3$	
		$PBr_5 \cdot BBr_3$	
		$P_2I_4 \cdot 2BBr_3$	

It is interesting that Tarible (31) found that phosphorus triodide and boron bromide do not react at ordinary temperatures. However, if they are heated in a sealed tube a mixture of large crystals of iodine along with yellow crystals in a colored liquid is obtained. The following reaction is reported to take place:

$$2PI_3 + 2BBr_3 \qquad P_2I_4 \cdot 2BBr_3 + I_2$$

A summary of the molecular compounds formed by the boron halides and the phosphorus halides is given in table 4.

Arsenic

No compounds have been reported in which arsenic is the donor atom to boron trifluoride. However, arsine is reported to form the compound $AsH_3 \cdot BCl_3$ with boron trichloride. Stock (25) found that arsine does not react with boron bromide at room temperature nor at 0°C., just as is the case with boron trichloride. It made no difference if the reactants were allowed to mix in the gas phase or if arsine were introduced into a solution of boron bromide in carbon disulfide. However, if boron bromide is dropped slowly into liquid arsine at a temperature between −100° and −80°C. (in the absence of oxygen and water and preferably in the presence of hydrogen) a white amorphous solid is obtained. The solid is very refractive and forms glittering colorless crystals when sublimed in a vacuum. The crystals appear under low-power magnification as right-angled plates and prisms, the edges of which cut off planes to give the appearance of hexagonal crystals. The crystals were found by analysis to have the composition $AsH_3 \cdot BBr_3$.

$AsH_3 \cdot BBr_3$ is oxidized by oxygen at temperatures above −40°C. and is spontaneously inflammable in air, yielding hydrogen bromide, boric oxide, and arsenious oxide. Upon heating, the compound decomposes completely without melting. In a sealed tube kept in the dark at ordinary temperatures the compound decomposes in several weeks, yielding boron bromide, hydrogen, and arsenic. This decomposition is accelerated by heat. However, at 90°C. no reaction occurs between the boron and arsenic such as occurs between boron and phosphorus when $PH_3 \cdot BBr_3$ decomposes.

$AsH_3 \cdot BBr_3$ hydrolyzes to form boric acid, hydrogen bromide, and arsine. There is no apparent reaction between the compound and sulfuric acid, but with nitric acid a violent oxidation occurs. Chlorine causes the compound to burn with a light blue flame, leaving a snow-like residue which Stock postulates might be a compound formed by boron chloride and arsenic trichloride. This is contrary to the results published earlier by Tarible (*vide infra*). With bromine, the compound burns with a pale yellow flame. At −50°C. the compound reacts with arsenic trichloride, yielding arsenic, hydrogen chloride, boron chloride, and arsenic tribromide.

The compound is soluble in its reactants but insoluble in carbon disulfide. At 10°C. the compound reacts with ammonia to form $9NH_3 \cdot 2BBr_3$ (*vide supra*).

Arsenic trichloride was found by Tarible (31) to enter into a double decomposition with boron bromide with the liberation of a considerable quantity of heat. He observed also that boron bromide dissolves arsenic tribromide at 18°C. but that no compound is formed. The iodides of arsenic (AsI_3 and AsI_5) are soluble in boron bromide at temperatures between 180°C. and 200°C., but no reaction occurs in a sealed tube.

Antimony

Tarible (31) extended his study to the compounds of antimony and observed that boron bromide enters into double decomposition reactions which are exothermic with antimony trichloride and antimony pentachloride, as indicated by the following equations:

$$SbCl_3 + BBr_3 \rightarrow BCl_3 + SbBr_3$$

$$3SbCl_5 + 5BBr_3 \rightarrow 5BCl_3 + 3SbBr_3 + 3Br_2$$

Antimony tribromide and antimony triiodide are soluble in boron bromide with an alteration of their properties.

GROUP VI

Oxygen

From the reactions of the above molecular compounds of boron bromide and boron iodide it is quite evident that these halides readily hydrolyze to give boric acid and the corresponding hydrogen halide. In this respect these boron halides are like boron trichloride. On the other hand, boron trifluoride with limited quantities of water under suitable conditions forms three hydrates. This is probably due to the fact that fluorine is more electronegative than the other halogens and therefore forms stronger bonds with the central boron atom, which in turn forms a stronger dative bond with oxygen.

The only inorganic compound which has been reported to form a coördination compound with boron bromide in which the donor atom is considered to be the oxygen atom is phosphoryl chloride (*vide supra*).

The reactions of organic compounds with boron bromide are analogous to their reactions with boron trichloride. Instead of forming coördination compounds, as is the usual case with boron trifluoride, boron bromide cleaves ethers. Benton and Dillon (1) have observed that diethyl, diisopropyl, di-*n*-butyl, isopropyl, phenyl, *n*-butyl phenyl, 2-bromophenyl methyl, mesityl methyl, and benzyl *n*-propyl ethers are cleaved by boron bromide to give the corresponding alcohol or bromide in accordance with the equations:

$$R_2O + BBr_3 \rightarrow (RO)_3B + 3RBr$$

$$(RO)_3B + 3H_2O \rightarrow 3ROH + H_3BO_3$$

Sulfur

Stock and Poppenberg (28) allowed boron bromide to react with cold hydrogen sulfide and obtained a white crystalline product. Hydrogen bromide was evolved. Better results were obtained, however, by allowing hydrogen sulfide to react with a solution of boron bromide in either benzene or carbon disulfide at 0°C. (25). Using a 50 per cent solution of boron bromide in carbon disulfide at its boiling point, white needle-like crystals of $B_2S_3 \cdot H_2S$ were obtained.

Working with Blix, Stock studied the reaction further by allowing hydrogen sulfide to pass through boron bromide for 10 to 12 days to obtain $B_2S_3 \cdot H_2S$ (26). The reaction was observed to proceed rapidly at first, owing to the formation of a crystalline compound composed of boron bromide and boron sulfide. The reaction then proceeds very slowly, owing to the decomposition of this compound by additional hydrogen sulfide. $B_2S_3 \cdot BBr_3$ is more easily obtained when $B_2S_3 \cdot H_2S$ is dissolved in an excess of boron bromide and dried in a vacuum. The compound remaining, $B_2S_3 \cdot BBr_3$, forms colorless crystals which melt above 100°C. and decomposes into its components when strongly heated. If boron bromide is introduced into a solution of $B_2S_3 \cdot H_2S$ in carbon disulfide while heating, $B_2S_3 \cdot BBr_3$ is formed. $B_2S_3 \cdot BCl_3$ is prepared in an analogous manner.

These reactions are different from the reactions obtained between hydrogen sulfide and boron trichloride and boron trifluoride at lower temperatures.

Under these conditions and using the method of thermal analysis, Germann and Booth (12) found evidence for the existence of $H_2S \cdot BF_3$ and Martin (20) for $H_2S \cdot BCl_3$. The above evidence indicates that boron bromide and boron chloride at higher temperatures tend to undergo solvolysis with hydrogen sulfide, whereas boron trifluoride has not been reported to react in this way. This is in line with the general fact that boron trifluoride is a much better acceptor molecule for the formation of coördination compounds than the other boron halide molecules. Owing to the great electronegativity of the fluorine atom, the boron atom in boron trifluoride is more positive than in the other boron halides and therefore has a greater affinity for a pair of electrons from a donor atom.

GROUP VII

Chlorine

Poggiale (23) allowed chlorine to react with boron bromide and discovered that the bromine atoms were immediately displaced.

The chlorine atom is considered to be donor in the compound $PCl_5 \cdot 2BBr_3$, discussed above.

Bromine

The system Br_2–BBr_3 was studied by Cueilleron (9, 10) and was found to contain no maximum but only a simple eutectic at 80 per cent boron bromide and −60.4°C., thus indicating that bromine has no tendency to donate electrons to boron bromide to form a molecular compound.

The bromine atom is considered to be the donor atom in the compound $PBr_5 \cdot BBr_3$, discussed above. It is interesting to note that this is the only compound reported in the literature in which a bromine atom is a donor to a boron atom of a boron halide.

SUMMARY

It has been observed that the number of coördination compounds formed by the boron halides increases inversely with their molecular weights. The properties of analogous compounds of these halides indicate that the electrophilic character of the boron atom in these molecules is strongest in boron trifluoride and becomes progressively weaker in the chloride, bromide, and iodide.

Compounds containing nitrogen, phosphorus, arsenic, oxygen, sulfur, chlorine, and bromine have been reported to act as donors to boron tribromide.

Boron iodide has been reported to form some compounds with ammonia only. These compounds are of unusual composition and their existence is somewhat doubtful.

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THE NATURE OF IODINE SOLUTIONS

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The results of the more significant studies concerning the nature of violet and brown iodine solutions are summarized. Although molecular weight determinations show that iodine is present in the diatomic state in all solvents, other physicochemical data, e.g., heats of solution, cryoscopic and distribution behavior, indicate that brown solutions contain iodine chemically bound to the solvent, in equilibrium with free iodine. Each of the compounds which form brown solutions with iodine contains an element capable of acting as a donor in the formation of coördinate covalent bonds.

Iodine in brown solutions appears to be much more reactive than the presumably free iodine in violet solutions. The results of reaction between iodine and certain silver compounds are described.

It is well known that iodine solutions may be either violet or brown, the color depending upon the solvent. This variation of color with solvent has intrigued many chemists, and has been the subject of numerous intensive investigations on solutions of iodine. The results of the more significant studies which have led to our present concepts of the nature of such solutions are summarized in this paper. Aqueous solutions containing complex ions of the nature of I_3^- present a separate problem which will not be considered here.

SOME PHYSICAL PROPERTIES OF IODINE SOLUTIONS

It was first demonstrated by Lachman (22) that iodine solutions made with pure solvents fall into two classes according to color,—violet and brown. Violet solutions are formed with such solvents as hydrocarbons, chloro- and bromohydrocarbons, and carbon disulfide, whereas alcohols, ethers, ketones, organic acids, nitriles, nitrogen bases, and certain sulfur compounds dissolve iodine to form brown solutions. Brown solutions tend to become violet when heated, and revert to their original color on cooling (22, 27); similarly, the violet color of an iodine–carbon disulfide solution becomes brown when the solution is cooled in a dry ice–ether bath (29). Precise molecular weight determinations by Beckmann (3, 5) have proved that iodine is present in the diatomic state in all solvents investigated. The apparently higher molecular weights obtained in certain instances by other investigators were due, according to Beckmann, to their failure to take into consideration the volatility of the iodine. Correction for this factor gives values which are in excellent agreement with the molecular weight of the diatomic form.

The data just cited appear to minimize the possibility of the presence in solution of free iodine molecules of a greater degree of complexity than I_2, in any significant concentration. On the other hand, it may be relevant to mention here the work of Rabinowitch and Wood (26) on the effect of light on solutions of iodine. In the case of solutions in carbon tetrachloride and in hexane, they concluded, from a study of extinction coefficients, that dissociation of iodine molecules into atoms occurred to a measurable extent under intense illumination. The fraction of monatomic molecules, however, never exceeded 1 in 2200, and the rate of recombination of atoms is very high.

Even though iodine exists almost entirely in the diatomic state in all solutions, the physical properties of the brown solutions differ markedly from those of the violet. In the first place, iodine is much more soluble, in general, in solvents giving brown solutions than in others. The classical investigations of Hildebrand and his students (18) have shown that the violet solutions form a series of "regular solutions."[1] In these cases, the variation of the solubility of iodine with temperature may be represented fairly accurately by a regular family of curves corresponding to the equation

$$\log N_2 = 2.264 - [876.5 + k(1 - N_2)^2] \times \frac{1}{T}$$

in which N_2 is the mole fraction of iodine in a solution saturated at the absolute temperature T, and k is a parameter, approximately independent of temperature for each solvent, whose value depends upon the energy of vaporization of the solvent. When k is relatively small, the curves obtained by plotting $\log N_2$ against $1/T$ are nearly linear except at temperatures approaching the melting point of iodine; as k becomes larger they take on a characteristic reversed S-shape. Approximate values of k for solutions of iodine in several solvents are as follows:

Solvent	CS_2	$CHCl_3$	$TiCl_4$	CCl_4	C_7H_{16}	$SiCl_4$
k	190	300	310	390	450	490

The fact that solubility curves for iodine in solvents in which it gives brown solutions do not fall in this family (nor, indeed, do they constitute a regular family of their own) indicates that new molecular species are formed in such solutions.

The distribution coefficient of iodine between its brown glycerol solution and its violet chloroform solution is influenced markedly by changes in temperature, whereas an approximately constant distribution coefficient is observed between two solvents in which iodine forms brown solutions (17). These facts are brought out in the data of tables 1 and 2. It is interesting to note in table 1 that the successive differences in the values of the distribution coefficients tend to become smaller as the temperature increases. This is not surprising, in view of the fact that brown solutions tend to become violet on heating.

The heats of solution of iodine in solvents giving brown solutions are much higher than the values for violet solutions (27). This fact is illustrated in table 3.

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[1] Regular solutions are defined as solutions which are formed from their components with the same change in entropy as occurs in the formation of an ideal solution of the same concentration.

Spectrophotometric studies give further interesting information concerning violet and brown solutions. The latter are transparent at the red end of the spectrum and absorb heavily in the violet, whereas the former absorb heavily in the longer wave-length portion of the visible spectrum and transmit both violet and all the infrared light beyond 1200 mμ (9). Violet solutions, moreover, have an absorption spectrum very similar to that of iodine vapor; and the spectrum of brown solutions at elevated temperatures, as would be expected, shows a shift in the absorption maximum toward the region of maximum absorption for violet solutions (21, 27). The work of Gróh (16) and particularly that of Getman (15) appears to indicate that for an iodine solution in a pure solvent at a fixed temperature only one of two colors is possible. Getman found, from measurements of the extinction coefficients in the visible spectrum of iodine solutions in purified solvents, that these solutions fall into two groups (table

TABLE 1

Distribution of iodine between glycerol and chloroform

t	CONCENTRATION IN GLYCEROL LAYER (c_1)	CONCENTRATION IN CHLOROFORM LAYER (c_2)	$c_1 + c_2$	$k = \frac{c_1}{c_2}$
°C.	*gram-moles/liter*	*gram-moles/liter*		
0	0.0119	0.0177	0.0296	0.675
10	0.0101	0.0198	0.0299	0.510
20	0.0084	0.0213	0.0299	0.410
30	0.0079	0.0217	0.0298	0.364
40	0.0077	0.0221	0.0297	0.349
50	0.0074	0.0226	0.0299	0.330

TABLE 2

Distribution of iodine between glycerol and ether

t	CONCENTRATION IN GLYCEROL LAYER (c_1)	CONCENTRATION IN ETHER LAYER (c_2)	$c_1 + c_2$	$k = \frac{c_1}{c_2}$
°C.	*gram-moles/liter*	*gram-moles/liter*		
0	0.00561	0.0270	0.0327	0.21
30	0.00544	0.0272	0.0326	0.20
30	0.00100	0.0051	0.0062	0.20

TABLE 3

Heat of solution of 1 g. of iodine in kilogram-calories

$CHCl_3$	CS_2	C_6H_6	$(C_2H_5)_2O$	C_2H_5OH	C_5H_5N
−21.52	−20.78	−18.36	−7.83	−7.58	+17.80
−21.65	−20.50	−18.51	−7.91	−7.75	+17.58

4): violet, with absorption maxima ranging from 520 to 540 mμ; and brown, with maxima from 460 to 480 mμ. The intensity of absorption also differs notably in the two groups. Getman also confirmed the observation of Ley and Engelhardt (23) that the absorption spectra of iodine solutions change with time.

The absorption spectra of solutions of iodine in several mixed solvents were studied by Weyl (28), whose results tend merely to confirm the earlier conclusions.

THE CONDITION OF IODINE IN BROWN SOLUTIONS

In order to account for the marked dissimilarities in properties between the brown and the violet solutions, it has been assumed by most investigators that the brown solutions contain iodine chemically bound to the solvent, in equilibrium with free iodine.[2] When the types of compounds which form brown solutions are considered in the light of our present knowledge of chemical binding, this assumption appears to be an altogether reasonable one. For it is readily apparent that each of these compounds contains an element, e.g., nitrogen, sulfur, or oxygen, capable of acting as a donor in the formation of coördinate covalent bonds.

TABLE 4

Absorption maxima and extinction coefficients of iodine solutions

VIOLET SOLUTIONS			BROWN SOLUTIONS		
Solvent	Absorption maximum	Extinction coefficient at maximum	Solvent	Absorption maximum	Extinction coefficient at maximum
	mμ			mμ	
n-C_6H_{14}	535	0.42	C_2H_5OH	480	0.30
C_6H_6	530	0.40	$(CH_3)_2CHOH$	480	0.27
$C_6H_5CH_3$	520	0.42	$(CH_3)_2CO$	460	0.23
CS_2	540	0.41	$CH_3COC_6H_5$	470	0.29
CCl_4	540	0.41	C_5H_5N	480	0.24
$CHCl_3$	535	0.41	H_2O	470	0.29
$C_6H_5NO_2$	500	0.42			

The case of iodine solutions in benzene is sufficiently anomalous to warrant special mention. Some observers have reported these solutions as brown, others as violet. It appears probable that the former statement was based upon observation of solutions in incompletely purified benzene, especially since a distinctly brown color is observed in thiophene solutions. Even in carefully purified benzene, however, the color is not a pure violet, at least at room temperature, but rather a violet-red, which changes to violet when the solution is heated. Hildebrand and Jenks (20) attribute the deviation of the solubility curve of iodine in benzene from its normal position in the regular family (18) to a slight degree of solvation, increasing with decreasing temperature. This hypothesis is supported by the work of Curti and Carbagnati (10), who infer the existence of a benzene–iodine complex from measurements of the dielectric constants of such solutions.[3]

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[2] An entirely different explanation of the brown color of iodine solutions in certain solvents was proposed by Amann (1), who stated that such solutions contained particles of colloidal dimensions, visible in the ultramicroscope. More recently, Chirnoagă and Chirnoagă (7) have contradicted this statement, so far as the presence of ultramicroscopically visible particles is concerned. They present evidence, however, based upon cataphoretic experiments, of the existence of iodine in a subultramicroscopic colloidal state (which they designate as cryptocolloidal) in solutions of iodine in 96 per cent alcohol. Their extension of this hypothesis, merely by analogy, to all iodine solutions which exhibit a brown color seems to us entirely unwarranted.

TABLE 5

Solvent effect on the freezing point of iodine–bromoform solutions

(Cryoscopic constant for bromoform = 13.8)

WEIGHT OF $CHBr_3$	SOLVENT ADDED	WEIGHT OF SOLVENT ADDED	WEIGHT OF IODINE	MOLAL LOWERING
grams		*grams*	*grams*	
20.80	$C_2H_4Br_2$	0.960	0.2370	13.8
36.45	CS_2	0.442	0.0885	13.7
19.12	$C_6H_5CHCl_2$	0.471	0.1692	14.0
20.99	CCl_4	0.457	0.0654	13.7
19.21	C_2H_5OH	0.117	0.0570	11.0
20.13	$C_6H_5CH_2OH$	0.478	0.0691	11.4
19.55	$C_6H_5NO_2$	0.444	0.1242	13.2

The most convincing proof of the existence of solvated iodine in brown solutions comes from the work of Hildebrand and Glascock (19), who studied the change in

[3] *Added in page proof:* The authors are greatly indebted to Professor Joel H. Hildebrand for the following private communication, which was received after this paper had been submitted for publication: "I have long wondered about the nature of the chemical interaction between iodine and benzene, evident from the shift of absorption of color away from the violet of unsolvated iodine. A possible explanation has appeared to lie in an acid–base interaction in the electron donor–acceptor sense such as we see in the union of I^-, the base, with I_2, the acid, to form I_3^-. Evidence of basic character in benzene is its union with BF_3, BCl_3, and with concentrated H_2SO_4. If this basic character is also responsible for its union with iodine, then the substitution of methyl groups should increase basic strength and ability to solvate iodine. That such a shift occurs in going from benzene to toluene solutions is shown in your table 4. As a further test, my collaborator, Dr. Hans A. Benesi, recently prepared iodine solutions of equal concentrations in benzene, toluene, xylene, mesitylene, and methylnaphthalene. We found that the color shifts stepwise in that order, ending with yellow. Dr. Benesi is at present engaged in measuring the absorption curves for these solutions. He has just found a strong absorption band for the benzene solution with a maximum at 3200 Å., which appears to correspond to a band with a maximum of 3530 Å. occurring in I_3^- solutions (W. R. Brode: J. Am. Chem. Soc. **48**, 1877 (1926)). The evidence at this moment appears to favor the acid–base explanation. The true explanation evidently is *not* to be found in dipole moments, because not only chloroform and 1,2-dibromoethane, but also 1,1- and 1,2-dichloroethanes and *cis*-dichloroethylene, recently investigated by Dr. Benesi (paper submitted for publication), all give violet solutions despite their considerable dipole moments."

the freezing point of solutions of iodine in an "inactive" solvent (i.e., one in which it gives a violet solution) brought about by the addition of a small amount of a third substance, itself either an "inactive" or an "active" solvent (i.e., one in which iodine gives a brown solution). In those cases in which the lowering is less than that calculated for the iodine on the basis of the dilute solution law, these authors conclude that there must be at least partial combination of iodine with the second solvent. The data of table 5 show that only with "active" solvents is a large deviation observed from the calculated freezing-point lowering.

By the same authors, the equilibrium for the reaction

$$I_2 + n(\text{“active” solvent}) \rightleftharpoons (\text{“active” solvent})_n \cdot I_2$$

was studied colorimetrically for various "active" solvents in several "inactive" media. The determination of free and bound iodine was based on the fact that violet solutions transmit violet light almost completely, while brown solutions absorb most heavily in this region of the spectrum. A mercury-vapor lamp was used as a source of light, and all red and green light was cut off from the box containing the colorimeter by means of appropriate filters. The amount of brown absorbing compound was determined in the presence of non-absorbing violet, by comparison of the intensity of the violet light transmitted by the mixture with that transmitted by a standard brown solution. A correction was made for the small amount of violet light absorbed by a violet solution.

TABLE 6

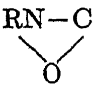
Study of the equilibrium $C_2H_5OH + I_2 \rightleftharpoons C_2H_5OH \cdot I_2$ *in carbon tetrachloride*

(c_1 concentration of alcohol; c_2 = concentration of iodine; c = concentration of complex)

$$K = \frac{c}{c_1^n \times c_2} \qquad 1$$

c_1	c_2	c	K
0.595	0.00153	0.00114	1.25
0.527	0.00164	0.00104	1.26
0.383	0.00188	0.00083	1.15
0.194	0.00221	0.00052	1.21
0.130	0.00236	0.00039	1.27

On the assumption that $n = 1$, good concordance was obtained in the values of the equilibrium constants in each case. The data for a typical equilibrium are given in table 6.

The nature of such molecular addition compounds of iodine as have actually been isolated is in agreement with the evidence given above for chemical binding between solvent and iodine in brown solutions. In each case, the compound adding to iodine contains an atom which can act as a donor in a coördinate covalent bond. Thus addition compounds of iodine with $(C_6H_5CH_2)_2S$, $(CH_3)_2S$, $(C_6H_5)_3CSC_6H_5$, C_5H_5N, C_9H_7N, and various substances of the general formula  $RN{-}CHR'$, have been prepared (4, 6, 8, 12, 14, 25, 27).

The precise nature of the binding between the iodine and the solvent molecule is not known in any instance. However, conductivity studies by Audrieth and Birr (2) have shed some light on the character of binding between iodine and pyridine. The electrical conductivity of solutions of iodine in pyridine increases with time. In very dilute solutions, however, a constant value is rapidly attained, the extremely high limiting value of approximately 130–132 units being found for the molecular conductance at infinite dilution. To explain the experimental data the authors postulate the gradual conversion of the initially formed non-conducting addition compound into a ternary salt, and believe it likely that solutions of iodine in pyridine contain the substances shown in the equilibria formulated below.

$$\mathrm{Py} + \mathrm{I_2} \rightleftharpoons \mathrm{IPy^+} + \mathrm{I^-} \rightleftharpoons \mathrm{Py^{++}} + 2\mathrm{I^-} \tag{a}$$

$$2[\mathrm{Py}\cdot\mathrm{I_2}] \rightleftharpoons \mathrm{IPy^+} + \mathrm{I}\cdot\mathrm{PyI_2^-} \tag{b}$$

Additional evidence in support of the hypothesis of such amphoteric behavior of iodine in brown solutions is to be found in the very recent work of Fairbrother (11) on the dielectric polarization of iodine in violet and brown solutions, respectively. The only results so far reported are given in table 7.

TABLE 7

Dipole moment of iodine in different solvents

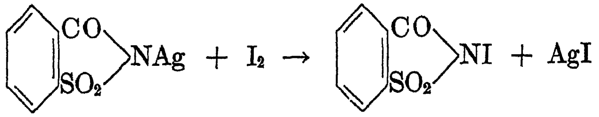
SOLVENT	COLOR OF SOLUTION	DIPOLE MOMENT OF IODINE (DEBYE UNITS)
C_6H_6	Violet-red	0.6
p-$C_6H_4(CH_3)_2$	Red	0.9
1,4-Dioxane	Brown	1.3
Diisobutylene	Red-brown	1.5

These results indicate that the formation of a red or brown solution is accompanied by polarization of the iodine molecule. It may be supposed that the proximity of an electron-donor stabilizes one of the possible ionic structures, I^-—I^+ and I^+—I^-, of an iodine molecule. Thus a partial ionization of the iodine takes place, the positive end of the molecule being stabilized by coördination with a molecule of the solvent.

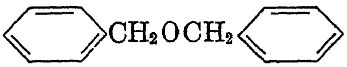
THE INFLUENCE OF SOLVENT ON THE REACTIVITY OF IODINE

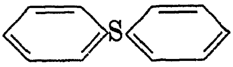
The bound iodine in brown solutions appears to be much more reactive than the presumably free iodine in violet solutions. It is possible, moreover, to activate the iodine in violet solutions by the addition of compounds which change the color of such solutions to brown.

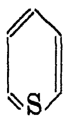
It has been shown by the determination of the iodine numbers of fats (24) that such compounds take up from violet solutions only about one-half the calculated quantity of iodine, whereas they take up from brown solutions the total amount theoretically possible. Furthermore, brown solutions of iodine in ether, alcohol, dioxane, cyclohexanol, and cyclohexene have been found to react with the silver derivative of saccharin to produce the theoretical quantity of silver iodide. When violet solutions of iodine in chloroform, benzene, carbon disulfide, carbon tetrachloride, and petroleum ether are treated with the same silver derivative, the first two behave, it is true, in the same manner as the brown solutions,[4] but the others react to a slight extent only (13). The reaction which takes place here is postulated to be the following:

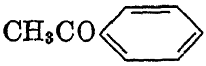


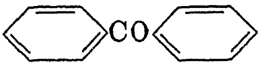
The activation of violet iodine solutions with respect to this reaction with the silver derivative of saccharin, by the addition of compounds which turn these solutions brown, has been investigated in some detail by Feigl and Bondi (12). Most of the compounds added markedly increase the reactivity of the iodine. Examination of the compounds which have been found to have little or no effect on the activity of iodine is of interest; they are

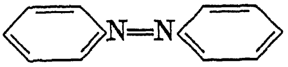












It is evident from the structures of these compounds that the potential donor atoms in the formation of coördinate covalent bonds with iodine would in these instances have but slight tendency to donate a pair of electrons. The deactivating influence of the benzene ring is a prime factor in this relative inability to form stable bonds. The observation has also been made that violet solutions of iodine in carbon disulfide are activated to a much smaller degree by methyl and benzyl ethers than by methyl and benzyl sulfides, respectively; this fact is in line with the lower electronegativity of sulfur.

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[4] Evidence has been obtained in our Laboratory to show that the completion of certain reactions between silver salts of carboxylic acids and iodine is dependent on the presence of chloroform. Its rôle, however, has not yet been completely determined. (Unpublished results of Zingaro, Kleinberg, and Vander Werf.)

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THE CHEMISTRY OF THE PYRROCOLINES AND THE OCTAHYDROPYRROCOLINES

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I. INTRODUCTION

Whereas the chemistry of the pyrrocolines so far has had a solely academic interest, that of the octahydropyrrocolines has received attention, mainly because of the suggested presence of the ring in several alkaloids. The difference has offered a natural subdivision for this review, and the pyrrocolines and octahydropyrrocolines will hence be dealt with separately.

II. THE CHEMISTRY OF THE PYRROCOLINES

The increasing interest shown in recent years in the chemistry of heterocyclic compounds has left the unusual pyrrocoline ring system comparatively unexplored. Hence, although it first received major attention at the hands of Scholtz in 1912 and onwards, possibly with the hope of devising a new source of dyes, it has failed so far to find a place in such a field. However, light-screening agents for photographic emulsions have been prepared in the form of polymethine dyes of 2-phenyl-, 2,3-dimethyl-, and 2-methyl-pyrrocolines by reaction with 2-βacetanilidovinylbenzoxazole ethiodide to yield (3-ethyl-2-benzoxazole) (pyrrocoline) dimethine cyanine iodides (16a).

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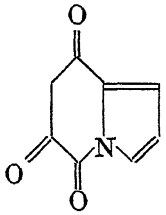
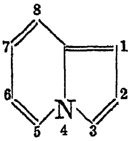
In 1890 Angeli (2, 3, 4) reported the preparation of the imine-anhydride of pyrroylpyruvic acid (I) and suggested that the completely unsaturated parent



I

base should be named pyrindole. However, other names—including pyrrodine, pyrrocoline, and indolizine—have been suggested since, and three systems of numbering (II, III, and IV) have been employed.



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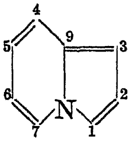

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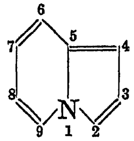
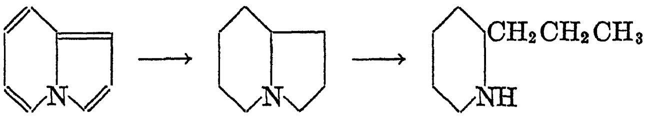


IV

Throughout this review the name pyrrocoline and the system of numbering (II) adopted by the American Chemical Society (75) will be used.

The parent base, pyrrocoline, was first synthesised by Scholtz (81), who obtained it by acid hydrolysis of a compound, $C_{12}H_{11}O_2N$, prepared by the treatment of α-picoline with acetic anhydride. The new compound, a colorless crystalline solid, m.p. 74°C. and b.p. 205°C., volatile in steam, had but feeble basic properties from which it was considered not to be a true derivative of pyridine. Furthermore, the compound gave, with isatin and with a pine splint, reactions typical of pyrroles; on fusion with oxalic acid it yielded a dark melt which produced a violet-red coloration in aqueous solution, a reaction typical of indoles. On this evidence, and in view of the fact that the compound possessed the same empirical formula (C_8H_7N) as indole and isoindole, Scholtz proposed the now accepted ring structure for his new compound.

Direct support for this formulation was produced by Diels and Alder (34), who demonstrated the presence of four double bonds by catalytic reduction of pyrrocoline to a derivative shown to be identical in all respects with δ-coniceïne (octahydropyrrocoline) previously prepared by Löffler *et al.* (63, 64). This, on degradation with cyanogen bromide, yielded *dl*-coniine (α-*n*-propylpiperidine).



dl-Coniine

Further evidence substantiating the pyrrolopyridine formulation for pyrrocoline arises from a consideration of the numerous syntheses described below.

III. SYNTHESES OF PYRROCOLINE AND ITS DERIVATIVES

A. Reaction of α-picoline and its derivatives with acid anhydrides

The reaction of acetic and of propionic anhydride with α-picoline and its derivatives may be described as a general method of preparing pyrrocolines by way of their acyl derivatives.

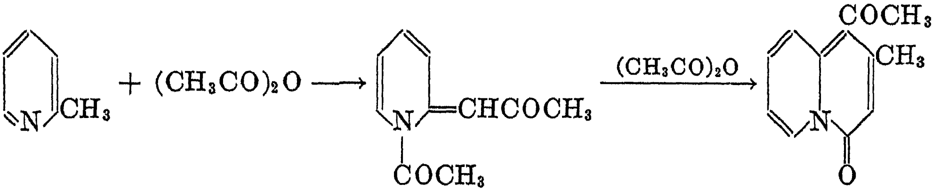
Scholtz (81) found that acetic anhydride and α-picoline at 200–220°C. yielded a crystalline compound, $C_{12}H_{11}O_2N$, which he called "picolide." The formation of this product corresponded to the following equation:

$$C_6H_7N + 2(CH_3CO)_2O \rightarrow C_{12}H_{11}O_2N + CH_3COOH + 2H_2O$$

The presence of one carbonyl group in "picolide" was readily demonstrated by the preparation of an oxime, a phenylhydrazone, and a semicarbazone, but it did not give reactions characteristic of aldehydes. It readily condensed with two molecules of aromatic aldehydes and underwent hydrolysis with 25 per cent hydrochloric acid to yield pyrrocoline, with the loss of two acetyl groups.

$$C_{12}H_{11}O_2N \rightarrow C_8H_7N + 2CH_3COOH$$

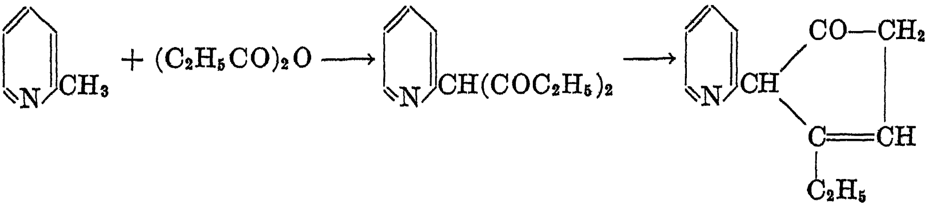
As "picolide" possessed no basic properties and failed to react in other precipitation reactions characteristic of organic bases, Scholtz and Fraude (84) assumed the nitrogen to be acylated and, having taken into account all its known properties, considered the most suitable structure to be 1-acetyl-2-methyl-4-ketopyridocoline (V), produced as follows:



V

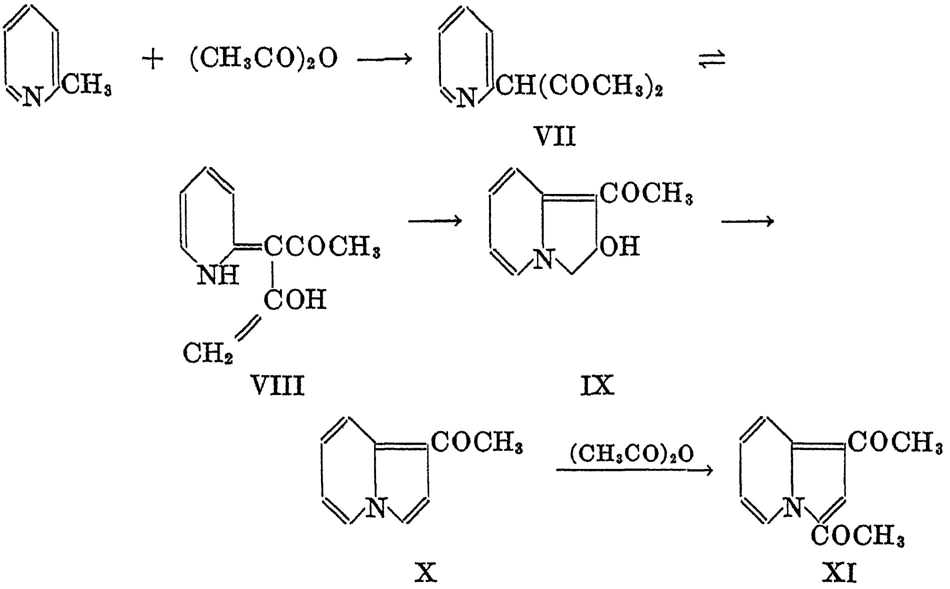
With this structure for "picolide" it was necessary to propose a complicated initial cleavage, followed by ring closure to a five-membered pyrrole ring, in order satisfactorily to explain its formation upon the hydrolysis of pyrrocoline.

This mechanism became untenable for the reaction of propionic anhydride with α-picoline, as here only one mole of anhydride was involved (84), yet the product still contained one reactive carbonyl group. A different mechanism was therefore proposed and the product was formulated as VI.



VI

These reaction mechanisms were unacceptable to Chichibabin and Stepanow (19), who claimed that the pyrrocoline nucleus was present in both products and that with acetic anhydride the reaction proceeded as follows:



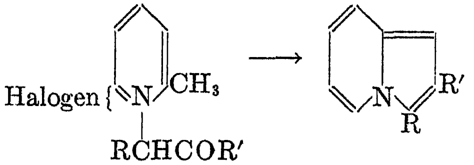
According to this mechanism the first product is the ω-diacetylpicoline (VII), which reacts in a tautomeric form (VIII) to undergo ring closure to 2-hydroxy-1-acetyl-2,3-dihydropyrrocoline (IX). Dehydration of the latter yields 1-acetylpyrrocoline (X), which is then further acetylated to produce "picolide" or 1,3-diacetylpyrrocoline (XI).

Similarly, the reaction of propionic anhydride with α-picoline was considered to produce 1-propionyl-3-methylpyrrocoline, which failed to undergo further acylation under the conditions employed. The apparent non-reactivity of the second acetyl group in "picolide" (XI) was not thought to detract from the validity of the new formulation, for derivatives of *N*-methylpyrrole containing an acyl group in the α-position do not readily undergo ketonic reactions (87). The presence of the pyrrocoline ring in picolide was finally substantiated by the monoacetylation of pyrrocoline, as described by Scholtz (82), to yield an acetylpyrrocoline, followed by further acetylation at 200°C. to yield picolide. Furthermore, monoacetylation of 2-methylpyrrocoline yielded an acetyl compound possessing no reactivity towards ketonic reagents under normal conditions. The presence of the pyrrocoline nucleus in the presumed 1-propionyl-3-methylpyrrocoline was demonstrated by deacylation to 3-methylpyrrocoline, the structure of which was finally established by Ochiai and Tsuda (73).

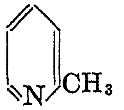
This mode of preparation has been extended to the use of α,γ-lutidine and α-phenyl-α-methylpyridine with acetic anhydride (83) to produce 7-methyl- and 5-phenyl-1,3-diacetylpyrrocoline, respectively, which on hydrolysis give 7-methyl- and 5-phenyl-pyrrocolines. Attempts to extend the reaction to other acid anhydrides (84) and to quinaldine with acetic anhydride (10) have met with failure.

B. Reaction of α-halogenoketones with pyridine bases

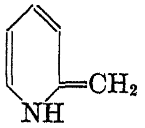
A more widely applicable method, which appears to be of considerable practical value for the preparation of pyrrocolines, is the ring closure of quaternary compounds formed from α-picoline and its derivatives and α-halogenoketones.



The existence of tautomerism in α- and γ-amino- and α- and γ-hydroxypyridines led Chichibabin (18) to suggest that a similar tautomerism could occur in α- and γ-alkylated pyridines. In particular, α-picoline on this theory would be expected to react either as the true α-methylpyridine (XII) or as α-pyridonemethide (XIII),

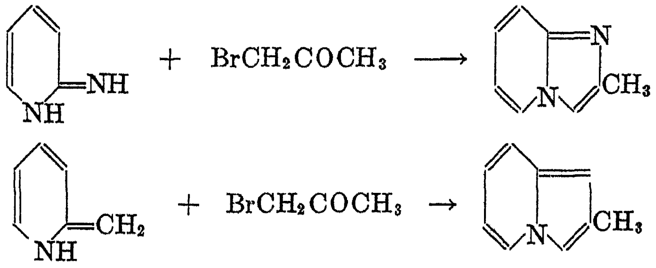


XII



XIII

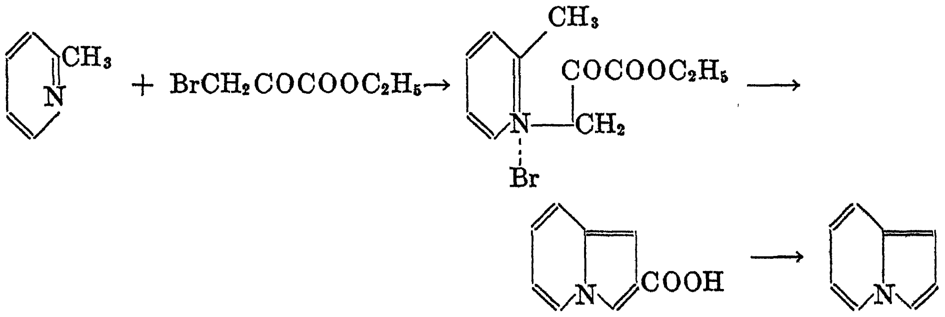
indicating the possibility of obtaining with form XIII ring closures similar to those already known for α-pyridoneimide, as represented by the following formulae:



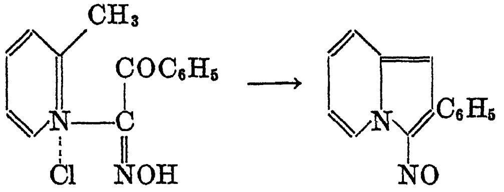
Theory was confirmed by the synthesis of 2-substituted pyrrocolines from bromo- and chloro-acetones and ω-bromoacetophenone, the quaternary picolinium compounds first formed undergoing ring closure to 2-methyl- and 2-phenylpyrrocolines on treatment with aqueous alkalis, preferably bicarbonate (11). Unfortunately, when the synthesis was attempted with an α-halogenated aldehyde, employing α-bromodimethylacetal, α-bromoacetaldehyde, and dibromoparaldehyde, the quaternary compounds from α-picoline were produced less readily and only with the second did pyrrocoline result on ring closure and then in very small yield.

The method has been applied satisfactorily to the preparation of 2,3-dimethyl-, 2,5-dimethyl-, 2-methyl-3-ethyl-, 1-phenyl-2-methyl-, and 2-phenyl-3-ethylpyrrocolines (14, 18, 73), and in some instances the preparation of the intermediate quaternary compounds by the procedure of King (49), from α-picoline, iodine, and the ketone, followed by ring closure, has been examined (11, 50). It is of interest that the substitution of quinaldine for α-picoline in the reaction with chloroacetone and ω-bromoacetophenone merely produced quinaldine hydrohalides (11) and none of the desired quaternary compound, a result which is in direct contradiction to a report (18) of Chichibabin. As to the influence of the nature of the α-halogenoketone on yields, there is evidence that bromo compounds are superior to chloro compounds (14) and that the yields drop progressively on substitution of the α-hydrogen by larger hydrocarbon residues (10, 11, 14).

Borrows, Holland, and Kenyon (9, 11) have attempted to extend the scope of the reaction to the preparation of acyl and carbalkoxy derivatives by the use of α-halogeno-β-diketones, α-halogeno-β-keto esters and a β-halogeno-α-keto ester, namely, α-chloroacetylacetone, α-bromobenzoylacetone, ethyl α-chloroacetoacetate, ethyl α-bromobenzoylacetate, and bromopyruvic acid or ester. With all but the last, difficulties arose at the quaternizing stage and on ring closure only 2-methyl- or 2-phenyl-pyrrocoline, respectively, could be isolated. However, ethyl bromopyruvate, and in poorer yield the acid, readily gave pyrrocoline-2-carboxylic acid. As this acid can be decarboxylated to pyrrocoline (32, 34), the method presents a new and possibly superior route to it.



Extension of this synthesis is exemplified by the preparation of ω-isonitrosophenacyl-α-picolinium chloride, from which 3-nitroso-2-phenylpyrrocoline arose in excellent yield (12).

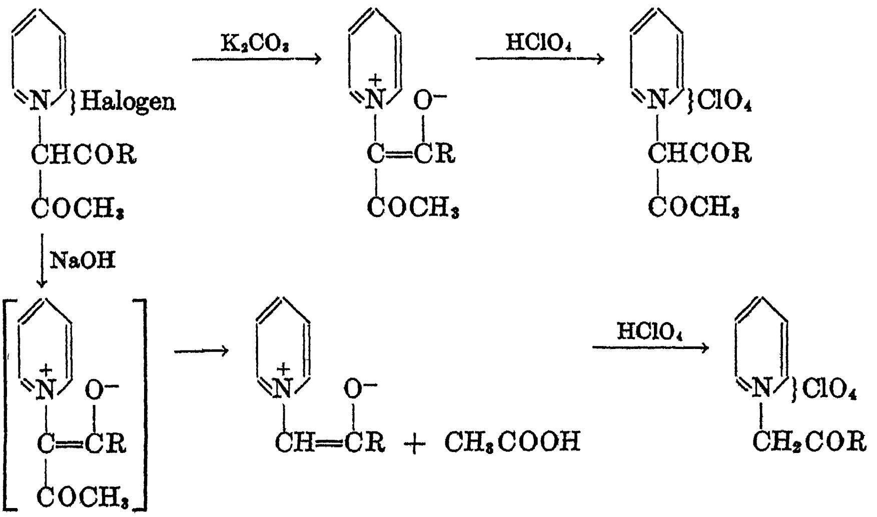


In contrast, the preparation of the corresponding quaternary nitro body from ω-nitrobromoacetophenone could not be effected (13).

A further variant of this method was attempted with the replacement of α-picoline by α-pyridyl-2-propanol and α-pyridylacetone, using ω-bromoacetophenone as the halogenoketone (8). In the first example no difficulty occurred in the preparation of the quaternary compound, but on attempted ring closure loss of the hydroxyethyl group resulted, with formation of 2-phenylpyrrocoline. Pyridylacetone, on the other hand, produced none of the desired quaternary product and to some extent acetone was cleaved from the base (10).

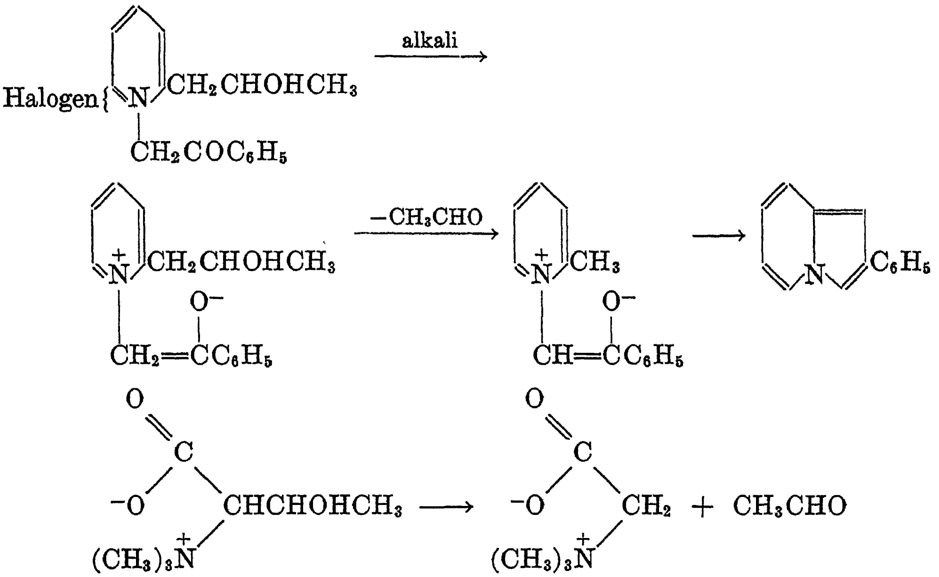
At this point an exposition of the possible mechanism of the Chichibabin synthesis seems appropriate. The behavior towards various alkaline reagents of quaternary compounds, formed from bases of the pyridine type with α-halogenoketones and β-diketones, has received considerable attention from Kröhnke *et al.* (56, 57, 58, 59, 60). These authors established that such quaternaries on treatment with alkalis of suitable strength yield "enol-betaines," which could undergo a so-called "acid cleavage" with loss of an acyl group, the smaller of the two present being lost by the quaternaries prepared from diketones. The over-all reaction can be effected directly by a more vicious alkaline treatment, weak bases such as potassium acetate or benzoate being ineffective.

The reactions with quaternaries from α-halogenodiketones are exemplified as follows:



This work therefore explains the advantage of using weak bases for the ring closure in the pyrrocoline synthesis and suggests "enol-betaine" formation as an intermediate step, during which acyl or carboalkoxy groups may be cleaved. This cleavage of the "enol-betaine" may occur also during the preparation of the quaternary compound, owing to the influence of the tertiary base. Thus, α-bromobenzoylacetone was reported (60) to yield α-phenacylpyridinium bromide on reaction with pyridine, and the failure of the similar reaction (11) with α-picoline to give on ring closure an acylpyrrocoline can probably be explained in this way. That the pyridine bases are capable at times of eliminating halogen acid from the related quaternaries with the possible formation of "enol-betaines" is shown by the formation (*a*) of benzoic acid from the reaction of ω-nitrobromoacetophenone with α-picoline, (*b*) of α-picoline hydrohalides as by-products in most of the preparations of the quaternaries, and (*c*) of quinaldine hydrohalides arising from the use of quinaldine with α-halogenoketones.

The loss of a hydroxyethyl group during attempted ring closure of phenacyl-α-pyridinium-2-propanol bromide probably results at the betaine stage by a retrograde aldol condensation in a manner analogous to the similar reaction reported to occur (17) on treatment of the betaines of threonine and allothreonine with alkali:

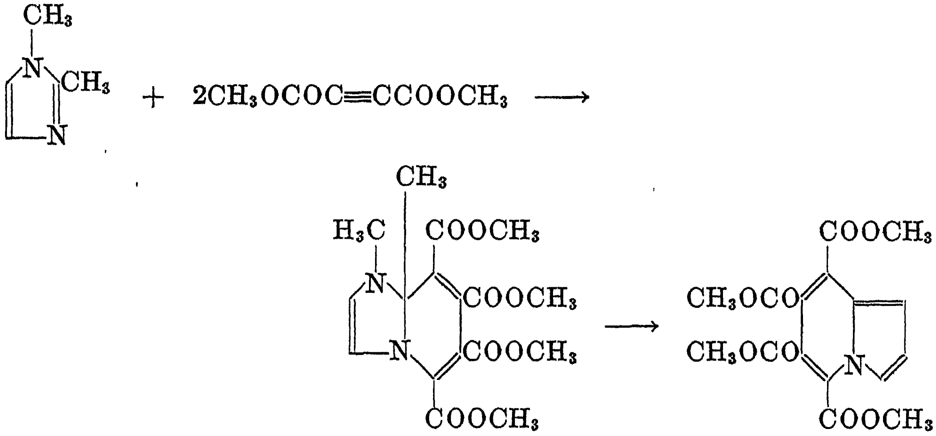


The stimulating review by Bergstrom (7) of the chemistry of pyridine, quinoline, and isoquinoline, based on the relationships of such heterocyclic systems to an ammonia system, suggests that α-pyridylacetone may be regarded as a "mixed" aquoketone-ammonoketone and hence related to α,β-diketones of the water system. On these grounds the loss of acetone (10) and the difficulty of preparing the desired quaternary upon treatment of α-pyridylacetone with ω-bromoacetophenone become understandable.

C. Reaction of pyridine bases with acetylenedicarboxylic esters

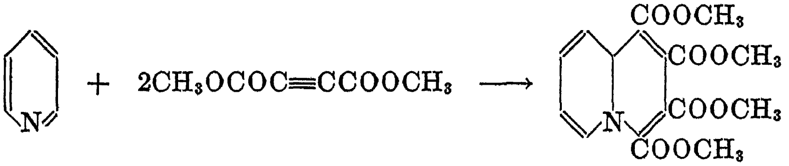
Diels and his collaborators have published a series of papers on the reaction of acetylenedicarboxylic esters with bases such as pyrrole, glyoxaline, pyridine, quinoline, isoquinoline, α-picoline, stilbazole, and quinaldine (32–34, 36–42, 69). From many of these investigations carboxylic ester derivatives of pyridocolines and, at times, of pyrrocolines were derived. As the former may be degraded conveniently to pyrrocolines, this work affords another general method for preparing pyrrocoline and its derivatives, especially carboxy and carbalkoxy compounds.

Dimethyl acetylenedicarboxylate on reaction with 1,2-dimethylglyoxaline yields tetramethyl 1,8-dimethyl-1,8-dihydropyrimidazole-4,5,6,7-tetracarboxylate, which on treatment with acetic acid loses methylamine to produce tetramethyl pyrrocoline-5,6,7,8-tetracarboxylate (XIV) (36).



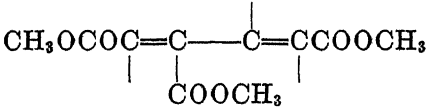
XIV

Pyridine (32, 33, 34) reacts similarly with dimethyl acetylenedicarboxylate in ether to yield tetramethyl pyridocoline-1,2,3,4-tetracarboxylate, a yellow "stable adduct" (XV).



XV

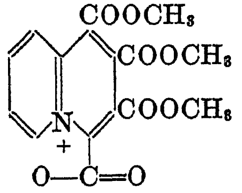
This product was considered to have arisen by the condensation of the pyridine N=C bond with the unsaturated chain,



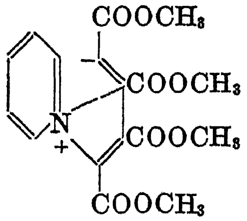
$$\mathrm{CH_3OCO\underset{|}{C}{=}\underset{\substack{|\\ COOCH_3}}{C}{-}\overset{\substack{COOCH_3\\ |}}{C}{=}\underset{|}{C}COOCH_3}$$

formed by the interaction of two molecules of the ester. That the initial condensation did not proceed by condensation of one molecule of ester to yield α-pyridylmaleate was evidenced by the observation that quinaldine, which possesses no α-hydrogen atom, condensed likewise with the ester (33, 38). Furthermore, in addition to the yellow "stable adduct" two other products were isolated;

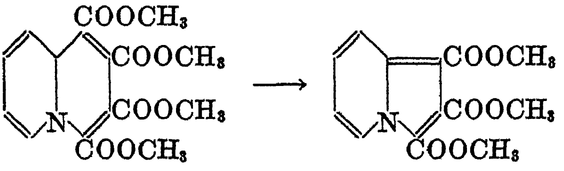
one, called the Kashimoto compound, was given the following formula:



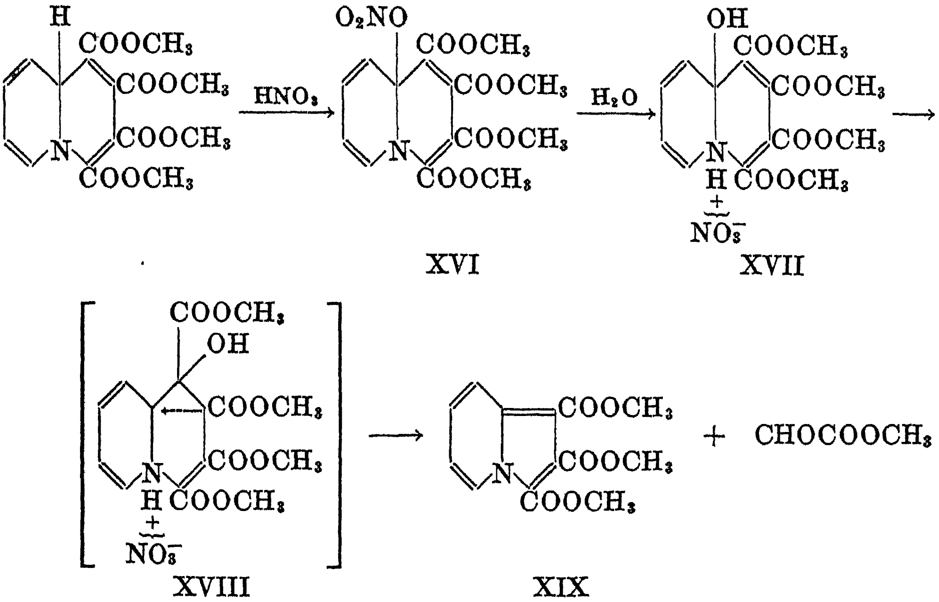
The second product, a red "labile adduct," could be converted readily into the yellow "stable adduct" by recrystallization from 50 per cent acetic acid or by heating. The "labile adduct" was an intermediate therefore in the formation of the "stable adduct," and it was shown by a considerable amount of unequivocal evidence to possess the following structure:



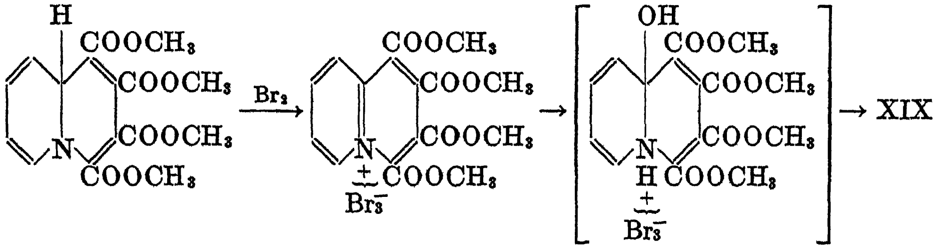
Oxidation of tetramethyl pyridocolinetetracarboxylate with nitric or chromic acid yields trimethyl pyrrocoline-1,2,3-tricarboxylate, and both compounds were shown to possess a pyridine moiety by oxidation with perhydrol in acetic acid to α-picolinic acid *N*-oxide.



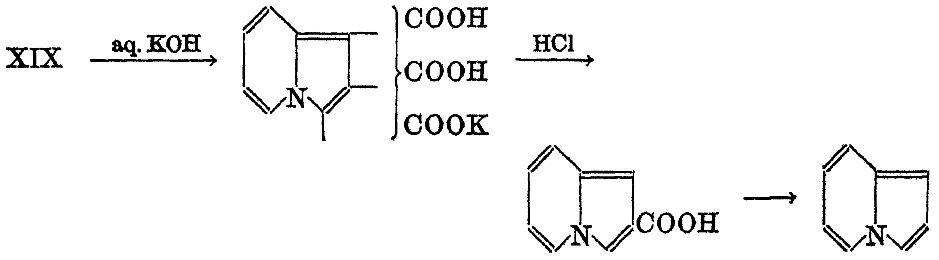
The mechanism of the chromic acid oxidation according to Diels and Alder is very obscure, but when nitric acid is employed, oxalic acid and intermediate products of the degradation can be isolated (32). Thus, treatment of the tetramethyl pyridocolinetetracarboxylate with concentrated nitric acid followed by evaporation produces a compound, $C_{17}H_{17}O_{14}N_3$, assigned the formula XVI, and this when treated with a limited quantity of water gives rise to a so-called "oxynitrate," $C_{17}H_{18}O_{12}N_2$ (XVII), which proves stable to hot water but on warming with dilute nitric or sulfuric acid yields trimethyl pyrrocoline-1,2,3-tricarboxylate (XIX). The last transformation was presumed to occur *via* a hydroxyl shift, yielding a hypothetical intermediate (XVIII), from which the pyrrocoline arose by cleavage of methyl glyoxalate.


XVI XVII XVIII XIX

The pyridocoline adduct can also be converted to the pyrrocolinetricarboxylate by the action of bromine, to yield a perbromide (XX) from which the pyrrocoline (XIX) arises on hydrolysis with loss of methyl glyoxalate. The reaction mechanism, involving a hypothetical "oxybromide" (XXI), is expressed as follows:

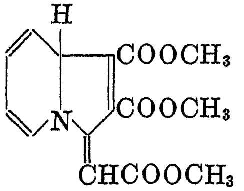

XX XXI

Hydrolysis of the trimethyl pyrrocoline-1,2,3-tricarboxylate with aqueous caustic potash yielded a monopotassium salt of the free acid, which on heating with dilute hydrochloric acid caused partial decarboxylation to produce a mono-

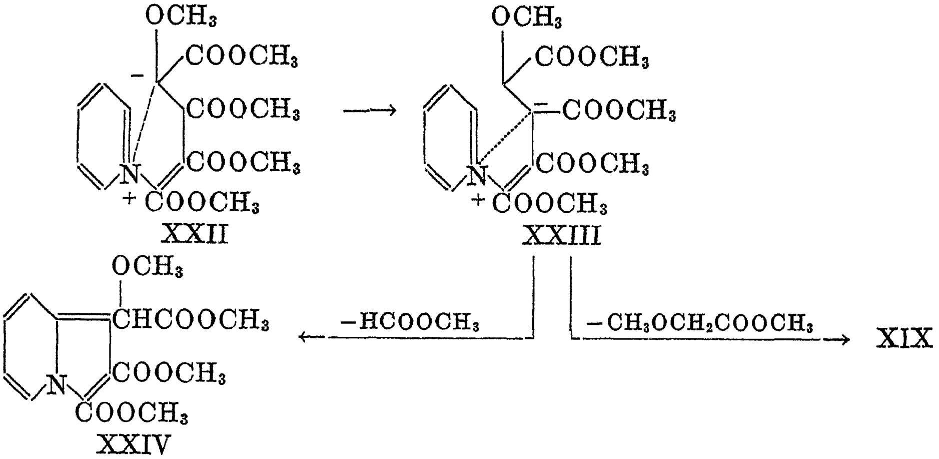


carboxylic acid; this on distillation with calcium oxide gave rise to pyrrocoline (32). The latter monocarboxylic acid has since been identified as pyrrocoline-2-carboxylic acid (9).

During the course of the above investigations much evidence accrued to show that the pyridocoline ring system could be degraded to pyrrocoline under much milder conditions than by the processes already mentioned. Thus, boiling tetramethyl pyridocolinetetracarboxylate with phenol or formic acid was shown to yield a pyrrocolinetricarboxylic ester (39) and not the pyridocoline derivative, as had earlier been thought. Furthermore, attempted preparation of pyridocoline itself by saponification and decarboxylation of the above tetracarboxylate gave rise to a crude product which after hydrogenation was shown by Diels and Schrum (42) to be a mixture of 3-methyloctahydropyrrocoline and octahydropyrrocoline. The transformation to a pyrrocoline ring system was thought by these authors to occur during the initial hydrolysis and decarboxylation, the structure of the resulting compound being as follows:

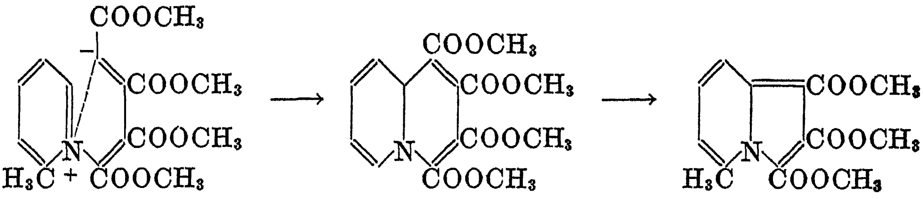


Unlike its action in ethereal solution, according to Diels and Meyer (39) the reaction of dimethyl acetylenedicarboxylate in methyl alcoholic solution with pyridine yielded derivatives of pyrrocoline directly. When the reaction was allowed to proceed unchecked, trimethyl pyrrocoline-1,2,3-tricarboxylate (XIX) resulted, whereas at 0°C. a "white adduct" arose and was shown to be dimethyl 1-methoxycarbomethoxymethylpyrrocoline-2,3-dicarboxylate (XXIV). Both of these products were considered to be formed from a common adduct (XXII) reacting *via* a hypothetical intermediate (XXIII), which was thought to lose either a molecule of methyl methoxyacetate or methyl formate to yield, respectively, XIX and XXIV.



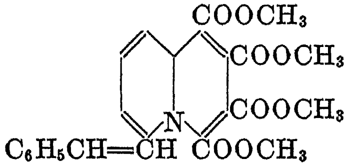
It was also reported that the "white adduct" (XXIV) could be successfully converted to XIX by treatment with bromine in methanol or acetic acid. There is a report (13), however, that an attempt to repeat the direct preparation of XIX resulted only in the formation of XXIV.

From the reaction of α-picoline with dimethyl acetylenedicarboxylate Diels and Pistor (41) isolated a yellow "labile adduct" (XXV), which was converted *via* the "stable adduct" (XXVI) to trimethyl 5-methylpyrrocoline-1,2,3-tricarboxylate (XXVII) by the usual methods.

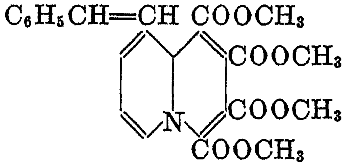


XXV XXVI XXVII

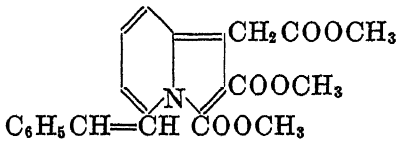
Similarly, stilbazole (40) yielded a "labile adduct" which could be converted to either of the two stable adducts XXVIII and XXIX.



XXVIII



XXIX



XXX

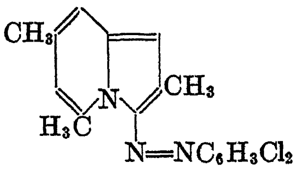
Trimethyl 5-styrylpyrrocoline-1,2,3-tricarboxylate was obtained from the "labile adduct" or from XXVIII on oxidation with chromic acid, but heating these with phenol or boiling alone was considered to yield XXX.

D. Other methods

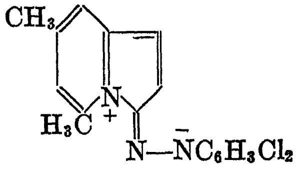
A synthesis of pyrrocoline which appears to be of little practical importance was reported by Brand and Reuter (15). Thus the reduction of 2-(γ,γ,γ-trichloro-β-hydroxypropyl)pyridine hydrochloride in aqueous sulfuric acid with zinc dust gave rise in small yield to 2-(γ-chloro-β-hydroxypropyl)pyridine, which on treatment with strong caustic soda yielded pyrrocoline.

Wilson (89) has reported the formation of pyrrocoline in small yield during the aluminum oxide catalyzed conversion of furan to pyrrole in the presence of ammonia.

Prolonged heating of collidine with the betaine-like compound arising from the action of pyridine with the imino-chloride of *N*-2,4-dichlorophenylpyruvic hydrazide gave rise to a red-brown product which was given either of the two alternative formulae XXXI and XXXII (68).



XXXI



XXXII

Only one attempt to dehydrogenate the octahydropyrrocoline ring system has been recorded in the literature. Prelog and Balenovič (76), employing palladized charcoal and selenium catalysts, failed to isolate any definite product from the dehydrogenation of octahydropyrrocoline.

IV. PROPERTIES

Pyrrocoline and all the known alkylpyrrocolines are either low-melting solids or high-boiling liquids, volatile in steam, unstable in air and light. On the other hand, with the attachment of an aromatic benzene ring at the 2- or 5-position stable solids non-volatile in steam result. All give colors in the pine splint test, characteristic of pyrrole, and colored melts on fusion with oxalic acid, a test characteristic of indole. A third diagnostic test is the treatment of the pyrrocolines in dilute sulfuric acid with a crystal of potassium iodate, when pyrrocoline and its 7-methyl and 5-phenyl derivatives produce deep indigo-blue colors (83). Many pyrrocolines in solution or as vapors or solids exhibit in sunlight or under ultraviolet light characteristic fluorescence. The ultraviolet absorption spectra of 2-phenylpyrrocoline and its 3-acetyl and 3-ethyl derivatives have been recorded (10, 14) (see Section XII).

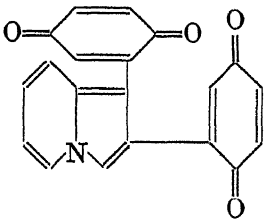
Alkyl- and aryl-pyrrocolines can be characterized quite satisfactorily by the preparation of the usual types of salts such as picrates, chloroplatinates, etc.

On present evidence it is difficult to assess the stability of the pyrrocoline nucleus to oxidizing agents. Thus there are reports (81, 83) that the parent base and its 7-methyl and 5-phenyl derivatives are sensitive to potassium permanganate and chromic oxide in sulfuric acid, but in comparison it is necessary to draw attention to the apparent stability of trimethyl pyrrocoline-1,2,3-tricarboxylate which arises from the oxidation of tetramethyl pyridocoline-1,2,3,4-tetracarboxylate (8, 32, 33, 34). Here, however, the reactive pyrrole ring is protected by the carboxylic ester groups. The successful oxidation of nitroso to nitro groups in the pyrrocoline nucleus has been effected under critical conditions with perhydrol (12, 13). This agent, however, rapidly attacks the nucleus and is thus useful for degradative purposes (Section XIII).

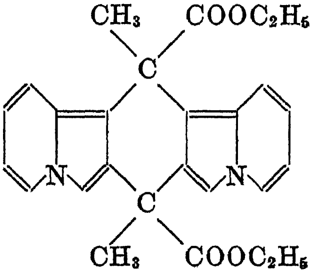
Whereas pyrrole reacts with isatin to yield the blue dye pyrrole indophenine (22) and a colorless crystalline compound (65), pyrrocoline in acetic acid with excess isatin produces a violet coloration and, with equal quantities, a colorless crystalline product of unknown constitution formed as follows (82):

$$2C_8H_7N + 2C_8H_5O_2N \rightarrow C_{32}H_{22}O_3N_4 + H_2O$$

Analogously to indole, pyrrocoline condenses with quinone to yield a diquinonylpyrrocoline formulated (82) as follows:



Also similarly to pyrrole and indole, pyrrocoline and its 7-methyl and 5-phenyl derivatives condense with aldehydes in alcoholic solution to yield dipyrrocolinylmethanes (81, 83), the exact structures of which are as yet undetermined. Whereas these products tend to become blue in air, those prepared from pyrrocoline itself with simple ketones in acetic acid appear to be quite stable. Ethyl acetoacetate also condenses (84) with pyrrocoline in alcoholic hydrochloric acid to produce a compound believed to possess the following structure:



V. ALKYL DERIVATIVES

Many of the procedures of synthesis outlined in Section III are adaptable to the preparation of alkyl derivatives. In addition, Scholtz (82, 83) claimed by analogy with pyrroles that two methyl groups were introduced directly into the pyrrole moiety of the parent base and the 7-methyl derivative by treatment in alcohol with methyl iodide at 120°C. The Clemmensen and Kishner–Wolff methods with suitable modifications (14) are suitable for reducing acyl to alkyl and aralkyl pyrrocolines.

VI. HALOGENO DERIVATIVES

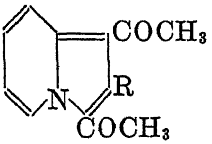
The reaction of halogens with pyrrocolines has received little attention. However, unstable and uncharacterizable crystalline compounds are reported to arise on treatment of pyrrocoline with bromine, and a diiodo compound of a similar nature is also recorded (84). Two unstable products were also obtained on addition of bromine to a chloroform solution of 1,3-diacetylpyrrocoline (81), corresponding to dibromo and tetrabromo compounds. In contrast, 3-acetyl-2-phenylpyrrocoline may be iodinated readily in alcohol to yield 1,3-diiodo-2-phenylpyrrocoline hydriodide and, in the presence of sodium acetate, 1-iodo-3-acetyl-2-phenylpyrrocoline (8).

VII. ACYL DERIVATIVES

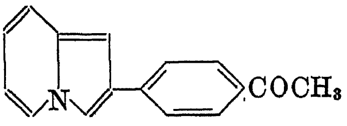
The direct synthesis of acylpyrrocolines would appear to be restricted to the action of acid anhydrides on α-picoline and its derivatives (81, 83, 84), as attempts to employ the method of Chichibabin, using halogenodiketones and α-picoline (11) or α-pyridylacetone and ω-bromoacetophenone (8), have been unsuccessful.

However, the pyrrocoline nucleus can readily be acylated by heating with acid anhydrides in the presence of the sodium salt of the corresponding acid. The monoacetyl derivatives of pyrrocoline (82), 7-methylpyrrocoline (83), 2-methylpyrrocoline (11, 19), and 2-phenylpyrrocoline (11), and the monobenzoyl derivative of 2-phenylpyrrocoline (11) have been prepared in this way. By further treatment with acetic anhydride at higher temperatures the monoacetyl derivatives of pyrrocoline (19), 2-methylpyrrocoline (11, 19), and 2-phenylpyrrocoline (11) have been converted to the corresponding 1,3-diacetyl compounds (XXXIII).

The application of the Friedel–Crafts reaction to the pyrrocoline nucleus has been successful in some instances. Ochiai (70) reported that 1,3-diacetyl-2-methylpyrrocoline (XXXIII, R = CH_3) could be prepared by the action of acetyl chloride on 3-acetyl-2-methylpyrrocoline in tetrachloroethane solution in the presence of a large excess of aluminum chloride, but only a very small yield of this compound could be obtained from 2-methylpyrrocoline itself and then only in carbon disulfide solution. With 2-phenylpyrrocoline, on the other hand, Borrows, Holland, and Kenyon (11) have found that reaction proceeds readily in carbon disulfide to yield a mixture of 1,3-diacetyl-2-phenylpyrrocoline (XXXIII, R = C_6H_5) and 2-*p*-acetylphenylpyrrocoline (XXXIV).



XXXIII



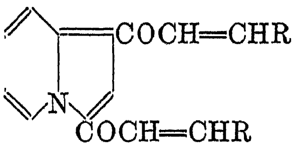
XXXIV

3-Acetyl-2-phenylpyrrocoline reacts well in tetrachloroethane solution to give the 1,3-diacetyl derivative. In the absence of the catalyst both acetyl chloride and acetyl bromide fail to react with 2-phenylpyrrocoline, an observation which is in marked contrast to the ready reaction of benzoyl chloride, which yields the same monobenzoyl derivative as that obtained by the action of benzoic anhydride. The facile reactivity of pyrrocoline itself with benzoyl chloride to yield a monobenzoyl derivative was also noted by Scholtz (84), who similarly obtained an unstable acid chloride by the action of phosgene on the parent base.

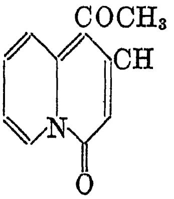
Acylpyrrocolines are reasonably stable, well crystalline solids, although Scholtz (82) recorded that 3-acetylpyrrocoline becomes green and finally blue on exposure to air and the 2-methyl derivative behaves similarly if impure (19). They give positive reactions in the pine splint test and colored melts on fusion with oxalic acid (14, 19) and, although Scholtz stated that 1,3-diacetylpyrrocoline ("picolide") possessed none of the properties of pyrrole (81), Chichibabin and Stepanow found that the homologous 1,3-diacetyl-2-methylpyrrocoline gave a slowly developing red color in the pine splint test (19).

The acyl groups are readily removed from these compounds by hydrolysis with mineral acids (11, 19, 20, 81, 83) and even boiling aqueous acetic acid is effective with 3-acetyl-2-phenylpyrrocoline (11). Diacyl derivatives appear to be somewhat more resistant than monoacyl derivatives (11) and those compounds containing a nitro (13, 82) or nitroso (12) group in the nucleus cannot be hydrolyzed in this way. 3-Acetylpyrrocoline has been reported to be stable to boiling alcoholic potash (82) but heating 3-acetyl-2-phenylpyrrocoline in alcoholic solution in the presence of sodium ethoxide at high temperature and pressure removed the acetyl group (14).

The condensation of aromatic aldehydes with 1,3-diacetylpyrrocoline in alkaline solution to give compounds of the type of XXXV has been carried out by Scholtz (81), who also obtained some monoarylidene derivatives; phenylacetaldehyde and *m*-hydroxybenzaldehyde failed to react (84). Similar derivatives have also been obtained from 1,3-diacetyl-7-methyl- and 1,3-diacetyl-5-phenylpyrrocolines (83) and 3-acetyl-2-methylpyrrocoline (11).



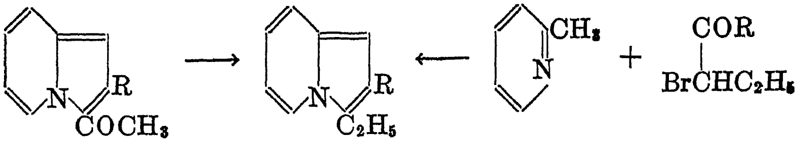
XXXV



XXXVI

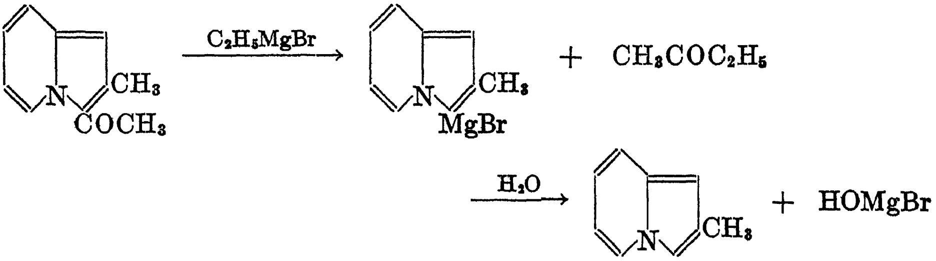
1,3-Diacetylpyrrocolines yield only mono derivatives with ketonic reagents (11, 19, 81, 83), a fact which led Scholtz to believe that "picolide" (1,3-diacetylpyrrocoline) did not contain a pyrrocoline nucleus and to ascribe to it the structure XXXVI (84). Chichibabin, however, prepared "picolide" by the stepwise acetylation of pyrrocoline (19), showing without a doubt that the pyrrocoline nucleus is indeed present in this compound.

Although 3-acetyl-2-methyl- and 3-acetyl-2-phenyl-pyrrocolines readily yield dinitrophenylhydrazones (11), none of the monoacetyl derivatives give rise to a phenylhydrazone or oxime under normal conditions except for the acetyl derivative of 7-methylpyrrocoline (83). From the lack of ketonic properties in these compounds Chichibabin assumed that the acetyl groups occupied the 3-position by analogy with the similar behavior of α-acetyl-*N*-alkylpyrroles. That this is so has been proved for the monoacetyl derivatives of 2-methyl- and 2-phenylpyrrocolines by reduction to their 3-ethyl derivatives and comparison with the compounds prepared by direct synthesis. Proof that the benzoylation of 2-phenylpyrrocoline also occurs in the 3-position has been established in a similar fashion (14). The reduction of the acyl groups in these compounds was effected by a modification of the Clemmensen method for 3-acetyl-2-methylpyrrocoline,

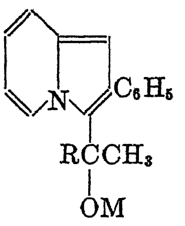


a mixture of the required 3-ethyl derivative and 2-methyl-3-α-hydroxyethylpyrrocoline being formed, and by Kon's modification (51) of the Kishner–Wolff method for 3-acetyl- and 3-benzoyl-2-phenylpyrrocolines (14).

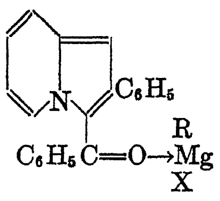
Chichibabin and Stepanow (19) recorded that the action of ethylmagnesium bromide on 3-acetyl-2-methylpyrrocoline gave rise to 2-methyl-3-ethylpyrrocoline, the same compound apparently being formed by the action of amalgamated aluminum in moist ether. However, the compound obtained was later shown by Kondo and Osowa (55) to be 2-methylpyrrocoline itself, and since methyl ethyl ketone was detected the reaction was considered to have taken the following course:



The present authors (8), working with 3-acetyl-2-phenylpyrrocoline, have recently shown that with a variety of organometallic compounds (RM) the reaction does not follow this course. The normal tertiary alcohol complex (XXXVIIa) is formed first, since it gives a negative result in the Gilman and Schultz test for carbon–metal linkages (47), and this breaks down to 2-phenylpyrrocoline and the methyl ketone ($RCOCH_3$) on hydrolysis. With 3-benzoyl-2-phenylpyrrocoline and methylmagnesium iodide it appears that a coördination compound of the type of XXXVIIb (46) is formed, since 3-benzoyl-2-phenylpyrrocoline was recovered on hydrolysis, but intramolecular rearrangement to the tertiary alcohol derivative occurred to some extent, for it was possible to isolate a small quantity of 2-phenylpyrrocoline and the ketone.



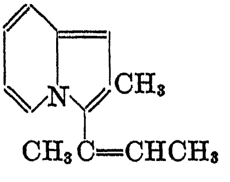
XXXVIIa



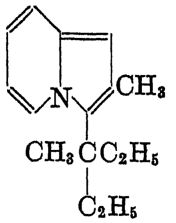
XXXVIIb

By using an excess of ethylmagnesium bromide on 3-acetyl-2-methylpyrrocoline Kondo and Kokeguchi (53) obtained, besides 2-methylpyrrocoline, 2-methyl-

3-(2-but-2-enyl)pyrrocoline (XXXVIII) and 2-methyl-3-(α-methyl-α-ethylpropyl)pyrrocoline (XXXIX). The former compound was considered to arise by loss of magnesium hydroxybromide from the normal tertiary alcohol complex and the latter by the addition of a further molecule of the reagent to the double bond of XXXVIII.



XXXVIII

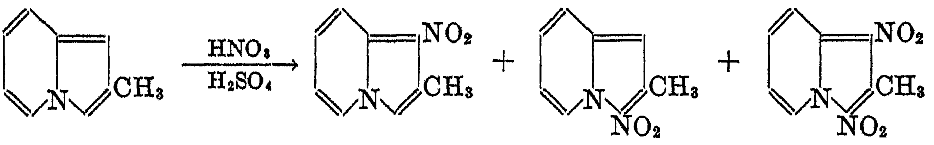


XXXIX

The action of Grignard reagents on diacylpyrrocolines was studied briefly by Scholtz and Fraude (84), who obtained monotertiary alcohols by the action of methyl- and phenyl-magnesium iodides on picolide.

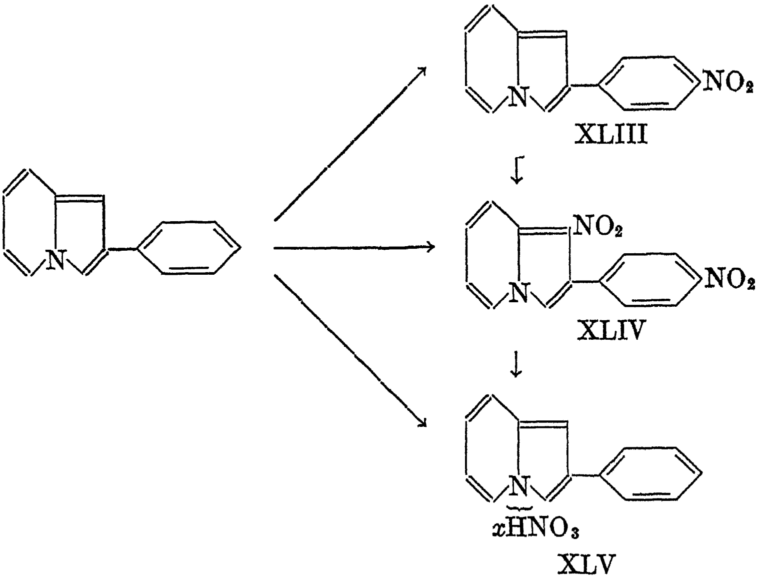
VIII. NITRO DERIVATIVES

Although Scholtz (82) prepared a nitroacetyl- and a dinitro-pyrrocoline by the action of nitric acid on 1,3-diacetylpyrrocoline, he stated that pyrrocoline itself could not be nitrated because of its sensitivity to oxidizing agents. However, work with 2-methyl- and 2-phenyl-pyrrocolines has recently shown (13) that it is possible to effect the direct nitration of this ring system for, while the action of nitric acid on these compounds at moderate temperatures caused mainly oxidation, rapid reaction at higher temperatures gave the 1,3-dinitro bodies in small yield in both instances. Furthermore, in concentrated sulfuric acid at low temperatures nitration was found to proceed readily with but little decomposition. Under these conditions 2-methylpyrrocoline yields 1-nitro-2-methylpyrrocoline (XL) as the main product, together with very small quantities of the 3-nitro isomeride (XLI) and 1,3-dinitro-2-methylpyrrocoline (XLII).



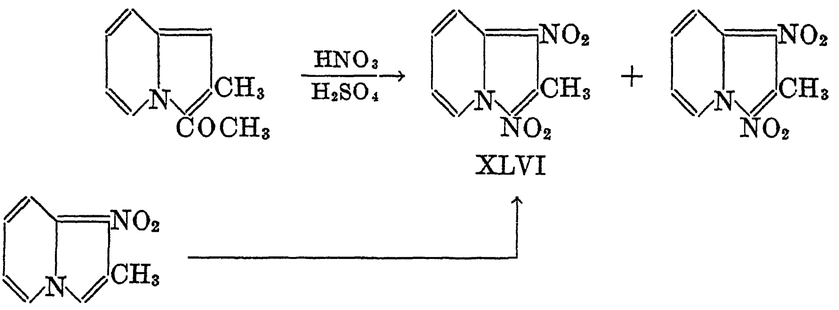
XL XLI XLII

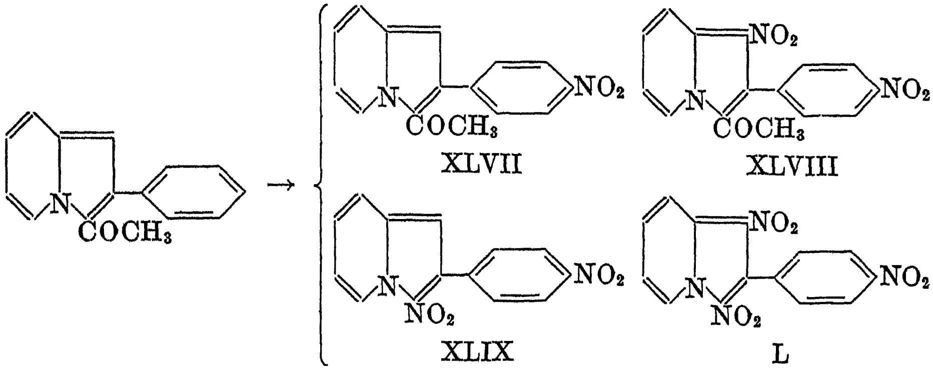
With 2-phenylpyrrocoline the benzene ring is attacked first to give 2-*p*-nitrophenylpyrrocoline (XLIII), a result which parallels the nitration of *N*-phenylpyrrole under similar conditions to yield *N*-*p*-nitrophenylpyrrole (31). The same compound is produced by nitration in phosphoric acid or by the action of sodium nitrate on a solution of the pyrrocoline in sulfuric acid. Further nitration of 2-*p*-nitrophenylpyrrocoline in sulfuric acid or dinitration of 2-phenylpyrrocoline in the same medium yields a dinitro body believed by analogy with the 2-methyl compound to be 1-nitro-2-*p*-nitrophenylpyrrocoline (XLIV), also formed by the dehydration of 2-phenylpyrrocoline nitrate (XLV) with sulfuric acid.



Further nitration of 1-nitro-2-methylpyrrocoline in sulfuric acid is accompanied by extensive decomposition and in hot acetic acid leads only to a small yield of 1,3-dinitro derivative. 3-Nitro-2-methylpyrrocoline is readily converted to the dinitro compound under the latter conditions.

The nitration of the 3-acetyl derivatives of 2-methyl- and 2-phenyl-pyrrocolines in concentrated sulfuric acid at low temperatures also proceeds readily. 3-Acetyl-2-methylpyrrocoline gives rise to 1-nitro-3-acetyl-2-methylpyrrocoline (XLVI), accompanied by a small quantity of the 1,3-dinitro compound, while 3-acetyl-2-phenylpyrrocoline yields a mixture of 3-acetyl-2-*p*-nitrophenylpyrrocoline (XLVII), 1-nitro-3-acetyl-2-*p*-nitrophenylpyrrocoline (XLVIII), 3-nitro-2-*p*-nitrophenylpyrrocoline (XLIX), and 1,3-dinitro-2-*p*-nitrophenylpyrrocoline (L). Three of these compounds (XLVIII, XLIX, L) are light sensitive, the yellow crystalline solids rapidly turning green on exposure to air and light.

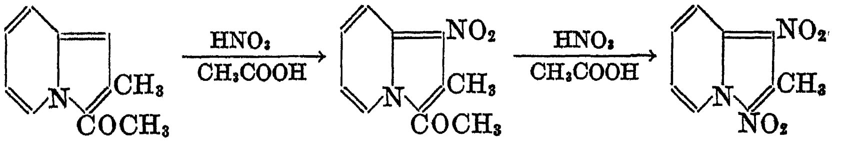




XLVII XLVIII XLIX L

1-Nitro-2-methylpyrrocoline can be acetylated to the 3-acetyl derivative (XLVI); hence the position of the nitro group in this compound is established, but 1-nitro-2-*p*-nitrophenylpyrrocoline (XLIV) could not be acetylated to the 3-acetyl derivative (XLVIII) nor could this compound be deacetylated by acid hydrolysis. The structures of the former compound and of the suspected 3-nitro isomeride (XLIX) have thus not been completely established.

The preparation of a nitroacetyl- and a dinitro-pyrrocoline was carried out by Scholtz (82) by the action of 25 per cent nitric acid and concentrated nitric acid, respectively, on an acetic acid solution of 1,3-diacetylpyrrocoline. As the 1,3-diacetyl derivatives of 2-methyl- and 2-phenyl-pyrrocolines behave similarly to yield the 1-nitro-3-acetylpyrrocolines with 25 per cent acid and 1,3-dinitro compounds with concentrated acid (13), the compounds prepared by Scholtz would seem to be similarly substituted. The action of excess concentrated nitric acid either alone or in acetic acid solution on the monoacetyl derivatives of 2-methyl- and 2-phenyl-pyrrocolines also gives the 1,3-dinitro compounds, but attempts to effect mononitration under the conditions used by Scholtz for 1,3-diacetylpyrrocoline were unsuccessful. However, with 3-acetyl-2-methylpyrrocoline it is possible to prepare 1-nitro-3-acetyl-2-methylpyrrocoline, thus showing that in acetic acid solution the 1-position is substituted before the acetyl group is replaced:



The nitroacetyl derivatives of 2-methyl- and 2-phenyl-pyrrocolines have also been obtained from the corresponding 1-nitroso-3-acetylpyrrocolines by careful oxidation with perhydrol (13), and 3-nitro-2-methylpyrrocoline has been prepared in small yield from the 3-nitroso compound in the same way (12). By the action of concentrated nitric acid on these nitroso derivatives the 1,3-dinitropyrrocolines are obtained.

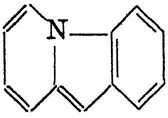
IX. NITROSO DERIVATIVES

The direct nitrosation of the pyrrocoline nucleus has been applied to 2-methyl- and 2-phenyl-pyrrocolines and their 3-acetyl derivatives and to 2-methyl-3-ethylpyrrocoline (12, 54) to yield the mononitroso compounds.

The 3-acetylpyrrocolines yield 1-nitroso derivatives, since on careful oxidation with perhydrol the corresponding 1-nitro-3-acetyl compounds are formed. Similarly, the derivative from 2-methylpyrrocoline has been shown to be the 3-nitroso body by its oxidation to 3-nitro-2-methylpyrrocoline. 3-Nitroso-2-phenylpyrrocoline cannot be converted to the nitro derivative in this way, but its structure has been ascertained by direct synthesis from ω-isonitrosophenacyl-α-picolinium chloride (12). The oxidation of the nitroso derivative from 2-methyl-3-ethylpyrrocoline to α-picolinic acid *N*-oxide confirms its structure as 1-nitroso-2-methyl-3-ethylpyrrocoline.

The acetyl groups could not be removed by acid hydrolysis from the above-mentioned compounds, nor could the 3-nitroso derivatives be acetylated.

The above nitrosopyrrocolines are green in color, but give yellow or red solutions in dilute acid, indicating that as cations they lose the true nitroso group (86). Further, both 3-nitroso-2-methyl- and 1-nitroso-2-methyl-3-ethyl-pyrrocolines are soluble in water to yield red solutions indicating that under these conditions also, they lose the true nitroso group. von Braun, Nelles, and May (16) record a similar phenomenon with the mononitroso derivative of benzo[*b*]-pyrrocoline (LI) and presumably, therefore, the nitroso group occupies the only free position in the five-membered ring of this compound. These compounds are not more soluble in alkali than they are in water.



LI

X. AMINO AND AZO DERIVATIVES

By the action of diazonium chlorides on pyrrocoline Scholtz and Fraude (84) obtained monoazo derivatives in which it was believed that the 3-position had been attacked. More recently Kondo and Nishizawa (54) have prepared 3-acetyl-2-methylpyrrocoline-1-azobenzene in a similar way and obtained 1-amino-3-acetyl-2-methylpyrrocoline by the catalytic reduction of the corresponding sodium azobenzenesulfonate. This same aminopyrrocoline was obtained by these workers by the catalytic reduction of 1-nitroso-3-acetyl-2-methylpyrrocoline and is the only known aminopyrrocoline. It is reported to be unstable in air.

Attempts to introduce an amino group into the pyrrocoline nucleus by reaction with sodium amide have been unsuccessful (10).

XI. CARBOXYLIC ACID DERIVATIVES

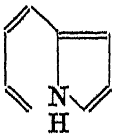
The preparation of carboxylic acid derivatives of pyrrocoline by the action of acetylenedicarboxylic esters on pyridine and other bases and the synthesis of pyrrocoline-2-carboxylic acid by ring closure of the quaternary compound formed by the action of ethyl bromopyruvate on α-picoline have already been discussed in detail (Sections III, B and III, C).

The direct introduction of a carboxyl group into pyrrocoline itself was effected by Scholtz and Fraude (84) by reaction with phosgene and treatment of the first formed unstable acid chloride with alkali. Reaction with ammonium carbonate or sodium bicarbonate under pressure, a method effective with many simple pyrroles (21), was unsuccessful however, and attempts to convert 2-methylpyrrocoline into pyrrocoline-2-carboxylic acid by fusion with potassium hydroxide (9), effective with skatole and 2-methylindole (23), were also unavailing.

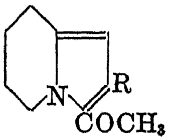
Condensation of 2-methylpyrrocoline with maleic anhydride yields a compound believed to be 2-methylpyrrocoline-1,3-disuccinic anhydride (52), as in the condensation with pyrrole to produce 2-methylpyrrole-5-succinic acid (35).

XII. REDUCTION

The reduction of the pyrrocoline nucleus was first attempted by Scholtz (81), who obtained a dihydro derivative on treatment of the parent base with sodium and alcohol. This compound, which gave a red color in the pine splint test but a colorless melt on fusion with oxalic acid, appeared to be a true pyrrole derivative, and Scholtz made the unlikely suggestion that it was α-butadienylpyrrole (LII), even though very energetic treatment with sodium and alcohol caused no further reduction. It seems more likely that the compound is a dihydropyrrocoline, the six-membered ring having been partially reduced, for tetrahydropyrrocolines have recently been obtained and behave similarly in the two color tests to the compound prepared by Scholtz. It seems reasonable to assume that the five-membered ring in them has not been reduced, since the positive pine splint test is indicative of the presence of a pyrrole ring (14).



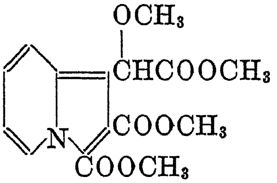
LII



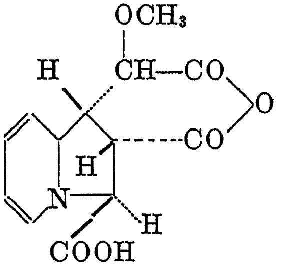
LIII

Thus, the hydrogenation of 3-acetyl-2-methylpyrrocoline at room temperature and pressure in the presence of platinum oxide as catalyst yields 3-acetyl-2-methyl-5,6,7,8-tetrahydropyrrocoline (LIII, R = CH_3) as the main product and similar treatment of the corresponding 2-phenyl derivative using Raney nickel gives the analogous compound (LIII, R = C_6H_5). The acetyl group in the last compound was readily removed by acid hydrolysis to yield 2-phenyl-5,6,7,8-tetrahydropyrrocoline as an unstable solid which could easily be reacetylated to the original compound (LIII, R = C_6H_5); the facility of the hydrolysis and reacetylation is further evidence for the ascribed structures. The reduction of 2-phenyl-3-ethylpyrrocoline in the presence of Raney nickel similarly yielded a tetrahydro derivative which gave a positive result in the pine splint test and was therefore considered to be 2-phenyl-3-ethyl-5,6,7,8-tetrahydropyrrocoline. This compound was also obtained, together with 2-phenyl-3-ethyloctahydropyrrocoline, by the reduction, under more vigorous conditions, of 3-acetyl-2-phenylpyrrocoline using copper chromite as catalyst.

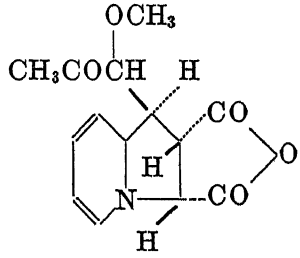
Although the above work indicates the preferential reduction of the six-membered ring of the pyrrocoline nucleus, Diels and Meyer (39) obtained evidence that in the reduction of methyl 1-methoxycarbomethoxymethylpyrrocoline-2,3-dicarboxylate (LIV), using platinum oxide as catalyst, the five-membered ring was reduced. Thus, on hydrogenation a tetrahydro compound was isolated which, after hydrolysis to the corresponding tricarboxylic acid and treatment with acetic anhydride, yielded an anhydride which differed from that obtained when the ester was hydrolyzed first and then hydrogenated. The composition of the latter compound indicated that it was a ketodicarboxylic acid anhydride, and it was conjectured therefore that the five-membered ring had been reduced in both instances, the formation of different anhydrides being due to *cis*- and *trans*-isomerism. The respective structures LV and LVI were suggested for these compounds.



LIV



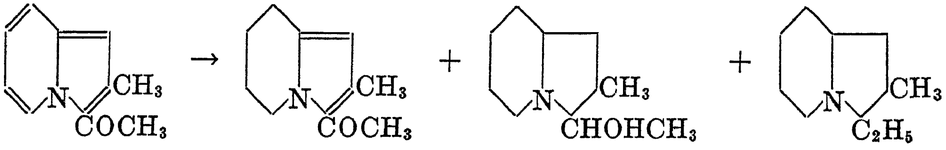
LV



LVI

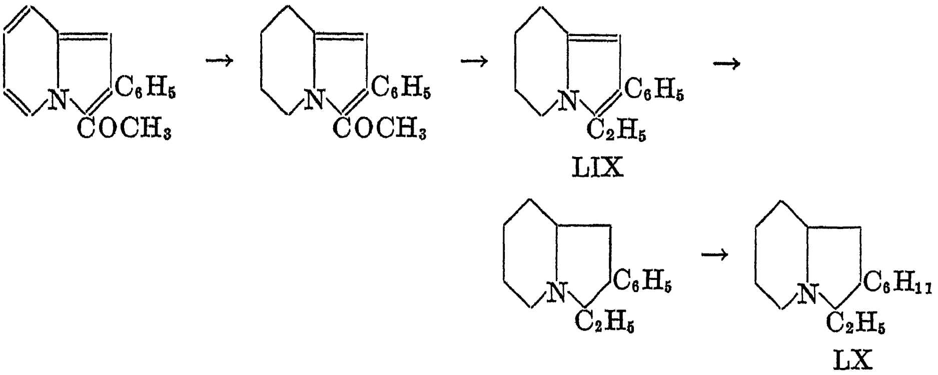
The reduction of methyl 1-nitropyrrocoline-2,3-dicarboxylate to an aminotetrahydropyrrocolinedicarboxylic ester was likewise considered by the above workers to involve the five-membered ring.

The complete reduction of the pyrrocoline nucleus has been reported by several workers. Pyrrocoline and 2-methyl-, 3-methyl-, 2,3-dimethyl-, and 2-methyl-3-ethyl-pyrrocolines have all successfully been converted to the octahydro compounds by catalytic reduction, using platinum oxide (14, 32, 34, 42, 73), and Ochiai and Kobayashi (72) obtained a mixture of 2-methyl-3-ethyl- (LVII) and 2-methyl-3-α-hydroxyethyl-octahydropyrrocolines (LVIII) by the hydrogenation of 3-acetyl-2-methylpyrrocoline under the same conditions. Borrows, Holland, and Kenyon (14), however, obtained only small quantities of these two compounds in this reduction, the main product being the tetrahydroacetyl derivative (LIII, R = CH_3) referred to above; complete reduction was best effected by using Raney nickel at high temperature and pressure.



LVIII LVII

3-Acetyl-2-phenylpyrrocoline similarly was readily converted to 2-phenyl-3-ethyloctahydropyrrocoline in this way, only small quantities of 2-phenyl-3-ethyl-5,6,7,8-tetrahydropyrrocoline (LIX) being produced. The formation of larger proportions of this last compound when using copper chromite as catalyst under comparable conditions is in agreement with the known tendency of this catalyst to effect the reduction of a carbonyl group rather than a C=C bond. Under more drastic conditions it was found possible to reduce 3-acetyl-2-phenylpyrrocoline to 2-cyclohexyl-3-ethyloctahydropyrrocoline (LX), using Raney nickel as catalyst, and it would appear that the stages in this reduction are as follows:



These results show some analogy with the catalytic reduction of substituted pyrroles, for, while it is well known that pyrrole is less susceptible to catalytic hydrogenation than is benzene or pyridine (1), Signaigo and Adkins (85) showed that its *N*-carbethoxy and *N*-phenyl derivatives could be reduced at much lower temperatures using Raney nickel as catalyst, *N*-phenylpyrrolidine being the major product in the latter instance. Rainey and Adkins (79), however, found later that *N*-methyl- and *N*-ethyl-pyrroles were nearly as resistant as pyrrole itself. It is not surprising that the six-membered ring, which has a pyridone structure, should be reduced before the pyrrole nucleus. The resulting tetrahydro compounds, which are, in effect, *N*-alkylated pyrroles, are presumably less resistant than is the benzene ring; hence in the phenyl derivatives the five-membered ring is preferentially reduced.

In connection with the elucidation of the structure of 2-phenyl-3-ethyloctahydropyrrocoline the ultraviolet absorption spectra of a few pyrrocoline derivatives have been examined. Whereas 2-phenyl- and 2-phenyl-3-ethyl-pyrrocolines exhibited in alcohol characteristic powerful absorptions, $\lambda_{max.} = 2570$ Å., $\epsilon = 45{,}700$ and $\lambda_{max.} = 2550$ Å., $\epsilon = 38{,}000$, respectively, 3-acetyl-2-phenylpyrrocoline has a spectrum consisting of three chromophores, $\lambda_{max.} = 2330$ Å., $\epsilon = 29{,}000$; $\lambda_{max.} = 2640$ Å., $\epsilon = 24{,}000$; $\lambda_{max.} = 3650$ Å., $\epsilon = 15{,}000$; $\lambda_{min.} = 2510$ Å., $\epsilon = 20{,}800$; $\lambda_{min.} = 3120$ Å., $\epsilon = 4000$ (10). The 5,6,7,8-tetrahydro derivative of the latter, however, possessed one maximum, $\lambda_{max.} = 3030$ Å., $\epsilon = 16{,}700$; $\lambda_{min.} = 2530$ Å.; $\epsilon = 5900$, and the corresponding 2-phenyl-3-ethyl-5,6,7,8-tetrahydropyrrocoline $\lambda_{max.} = 2780$ Å., $\epsilon = 7700$; $\lambda_{min.} = 2660$ Å., $\epsilon = 6960$ and inflection $= 2300$ Å., $\epsilon = 11{,}000$ (10).

Scholtz has recorded that the pyrrocoline ring is resistant to the reducing action of zinc and hydrochloric acid (81) and that hydrogenation using palladized charcoal as catalyst proceeds slowly (10).

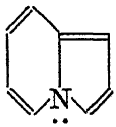
XIII. OXIDATION AND DEGRADATION

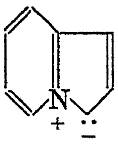
Although Scholtz (81) was unable to isolate α-picolinic acid by permanganate oxidation of 1,3-diacetylpyrrocoline, Diels and Alder (34) found that trimethyl pyrrocoline-1,2,3-tricarboxylate could be oxidized with a mixture of perhydrol and acetic acid to α-picolinic acid *N*-oxide. This reaction was used later by Diels and Meyer (39) to show the absence of a nitro group in the six-membered ring of dimethyl 1-nitropyrrocoline-2,3-dicarboxylate and has been successfully used subsequently by Borrows, Holland, and Kenyon (11–14) in orientation studies on derivatives of 2-methyl- and 2-phenyl-pyrrocolines. Diels and Meyer also showed that oxidation with nitric acid yields α-picolinic acid by its action on 1-methoxycarboxymethylpyrrocoline-2,3-carboxylic acid.

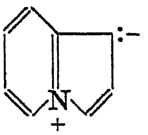
The complete reduction of a pyrrocoline to its octahydro derivative followed by degradation with cyanogen bromide has also proved useful in establishing structures in this field, and was employed by Diels and Alder (34), Ochiai and Tsuda (73), and Diels and Schrum (42) on pyrrocoline and its alkyl derivatives. It would appear that degradation with cyanogen bromide results in the selective cleavage of the five-membered ring of the octahydropyrrocolines to yield alkylpiperidines and not alkylpyrrolidines, but Diels and Schrum obtained evidence that with 2-methyloctahydropyrrocoline cleavage of the six-membered ring took place to some extent.

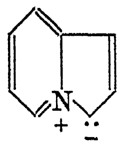
IV. CONCLUSIONS ON THE CHEMISTRY OF THE PYRROCOLINES

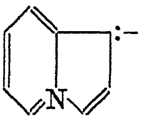
The application of the theory of resonance to explain the stability of pyrrole and similar heterocyclic compounds (66) has been extended to the pyrrocoline ring system by Wilson (89) (*cf.* also Ochiai (74)), and there can be little doubt that its aromatic character can be attributed to the unshared electrons on the nitrogen atom resonating among all the atoms of the ring, the true structure being a resonance hybrid of the following forms:

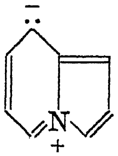

LXI

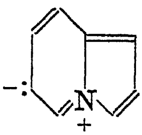

LXII

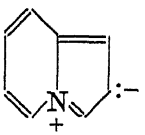

LXIII

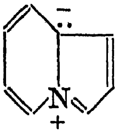

LXIV


LXV

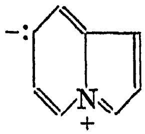

LXVI


LXVII

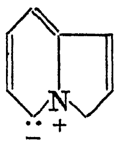

LXVIII



LXIX

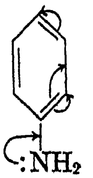


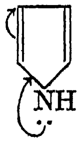
LXX

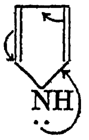


LXXI

Pyrrocoline, like pyrrole and indole, is much more reactive towards the usual cationoid reagents than is benzene, which again can be attributed to the presence of unshared electrons on the nitrogen atom. In pyrrole Robinson (80) has pointed out that the β-positions are analogous to the ortho positions of aniline or phenol, while the α-positions are analogous to the para positions.







In the pyrrocoline nucleus similar activation of all the positions in the two rings by the lone pair of electrons apparently does not occur, since the bulk of the evidence indicates that only the five-membered ring is attacked by electrophilic reagents. This can be explained by the reasoning used to account for the chemical reactivity of naphthalene (45), for examination of the above electronic structures for pyrrocoline shows that four forms (LXII, LXIII, LXIV, LXV) allow of an unshared pair of electrons on the 1- and 3-positions, while for each of the other positions of these electrons only one form can contribute. Thus the five-membered ring, and in particular the 1- and 3-positions, will be polarized by the attacking group and substitution will occur there. An alternative explanation is that in the forms LXII, LXIII, LXIV, and LXV resonance of the Kekulé type can take place in the six-membered ring without decreasing the number of double bonds in the five-membered ring, and hence these forms make the greatest contribution to the resonance hybrid structure. This view is in contrast to that put forward by Wilson, who stated that the Kekulé type of resonance could not occur in the pyrrocoline nucleus. It is noteworthy that similar considerations for the indole nucleus show the β-position to be the most reactive, a result which is in agreement with the general reactions of this ring system.

That the 1- and 3-positions are indeed reactive has frequently been established and the ready loss by acid hydrolysis of the carboxyl groups in the 1- and 3-positions but not in the 2-position of pyrrocoline-1,2,3-tricarboxylic acid affords further evidence of an increased electron density at the 1- and 3-positions by analogy with the similar ready decarboxylation of *o*- and *p*-hydroxybenzoic acids which Fieser and Fieser (44) have explained by the tendency of the hydroxyl group to increase the electron density at the carboxylated positions.

On calculation of the π-electron densities and bond orders in pyrrocoline Longuet-Higgins and Coulson (64a) found that position 3 had a much higher electron density than position 1, the latter being higher than for the 2-position in pyrrole. They anticipated therefore that the molecule would be readily attacked by cationoid (electrophilic) reagents first at position 3 and then at position 1, and if both were blocked, at positions 2 and 5. Their predictions are therefore verified by the chemistry reviewed herein.

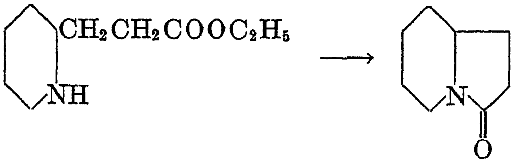
It would appear then that, while the chemical reactivity of pyrrocoline is, in general, similar to that of pyrrole and of indole, the position of ingoing substituents cannot be arbitrarily determined by analogy with these compounds. Thus the supposition made by Scholtz that aldehydes and ketones and similar compounds react with pyrrocoline at the 1- and 2-positions (the two β-positions) because pyrrole and indole react in this way is probably untrue, reaction occurring at the 1- and 3-positions. The formation of a dimethylpyrrocoline rather than a trimethylpyrrocoline by reaction with methyl iodide can be explained in this way, as can the formation of a diacetyl- rather than a triacetyl-pyrrocoline in Scholtz's "picolide" synthesis. On the other hand, it would seem that comparison of the 3-position of the pyrrocoline nucleus with the α-position of pyrrole is generally sound and has, in fact, been established in some instances.

Other differences between pyrrocoline and pyrrole and indole also become apparent from the above review. For example, the ready nitration of the pyrrocoline nucleus and the formation of true nitroso derivatives by the direct action of nitrous acid are rarely successful in the other ring systems.

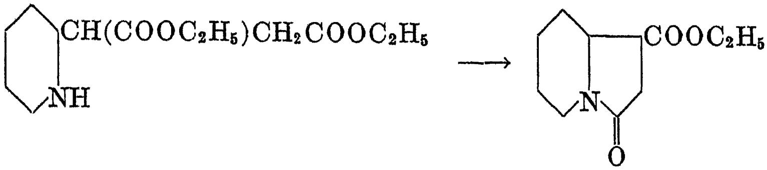
XV. OCTAHYDROPYRROCOLINES AND OTHER REDUCED FORMS OF PYRROCOLINES

A. Octahydropyrrocolines

One of the six coniceïnes obtained in various ways from the hemlock alkaloids is *l*-δ-coniciëne, an optically active (levorotatory) tertiary base arising from the action of concentrated sulfuric acid at 130°C. on *d*-*N*-bromoconiine (61). The compound was characterized in 1890 by Lellmann, who ascribed to it an octahydropyrrocoline structure. This formulation was confirmed by Loffler *et al.* (63, 64), who showed the inactive base, δ-coniceïne, prepared from *dl*-coniine, to be identical in all respects with octahydropyrrocoline, which they synthesized by the following methods: In addition to the preparation of octahydropyrrocoline (δ-coniceïne, piperolidine) from *N*-bromo-*dl*-coniine, they prepared the compound by the action of phosphorus pentoxide or a mixture of sulfuric and acetic acids on 2-γ-hydroxypropylpiperidine, by the action of hydriodic acid and phosphorus to yield iodoconiine (2-γ-iodopropylpiperidine), which underwent ring closure on treatment with alkali, and by reduction with sodium and alcohol of 3-ketoöctahydropyrrocoline (piperolidone) (II). The latter was obtained by distillation of β-piperidylpropionic acid, a ring closure which Clemo and Ramage (36) preferred to effect on the corresponding ethyl ester (I).



I II

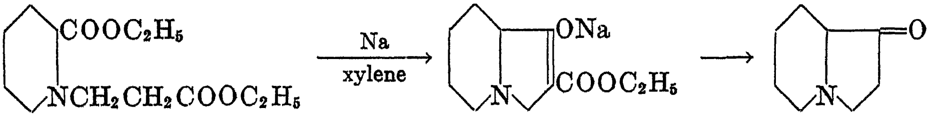


III IV

The method has been extended (27) to the preparation of the 1-carbethoxy-3-keto derivative (IV) by distillation of III.

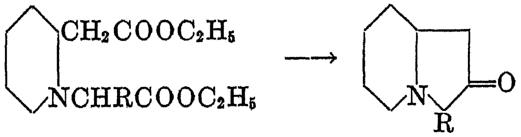
Beets has reported that reduction of β-(2-pyridyl)propionaldehyde diethylacetal in dilute acetic acid solution with platinum as catalyst yielded octahydropyrrocoline rather than the piperidylaldehyde produced in concentrated solution (6); the pyrrocoline picrate was obtained also by reduction in hydrochloric acid solution containing picric acid (5). On the other hand, reduction of ethyl β-(2-piperidyl)acrylate with Raney nickel as catalyst yields 3-ketoöctahydropyrrocoline (88).

In connection with the structure of lupinane and other alkaloids Clemo and his colleagues have synthesized several keto derivatives of octahydropyrrocoline. Thus, the 1-keto compound (VI) was obtained (24, 29) by the Dieckmann condensation of the requisite piperidyl ester (V) followed by hydrolysis and decarboxylation.

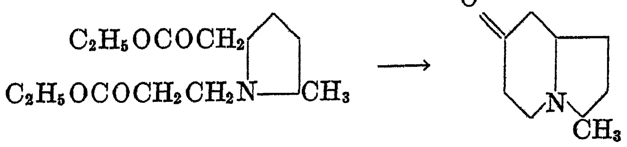


V VI

Similarly (24, 26) from VII (R = H or CH_3) arose the 2-keto derivatives VIII (R = H or CH_3).



VII VIII

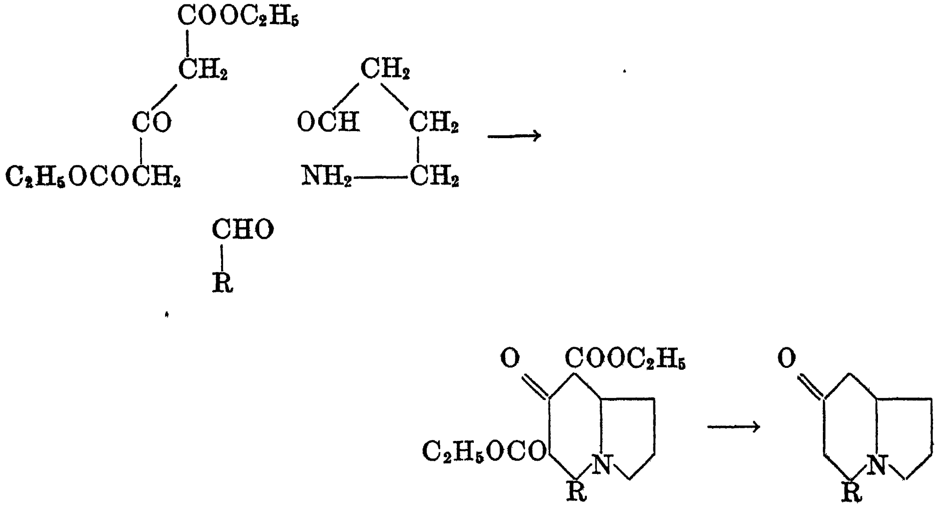


IX X

The condensation was successfully extended (25) to the pyrrolidine ester (IX) to give 3-methyl-7-ketoöctahydropyrrocoline (X).

Prelog and Metzler synthesized 6-ethyloctahydropyrrocoline by one of the methods employed by Loffler *et al.* (*vide supra*) for preparing the parent compound, involving alkaline ring closure of 2-(γ-bromopropyl)-5-ethylpiperidine (77).

An elegant synthesis devised by Lions and Willison (62) produces 5-alkyl- and 5-aryl-7-ketoöctahydropyrrocolines in excellent yield. The method involves the simultaneous condensation of an aldehyde, acetonedicarboxylic ester, and γ-aminobutyraldehyde to give unstable dicarboxylic esters (XI) from which the stable keto derivatives (XII) may be readily obtained. The yield of XI for aliphatic aldehydes is of the order of 90–95 per cent.



R = H, CH_3, sec-C_4H_9, C_6H_5

XI

XII

It will be noted that most of the syntheses yield keto derivatives. Of these, Clemo and Metcalfe (24) have employed the 1- and 2-ketoöctahydropyrrocolines for the preparation of alkyl derivatives, by reacting with methyl- or ethyl-magnesium bromide to yield the secondary carbinols which on dehydration by phosphorus pentachloride or potassium hydrogen sulfate gave hexahydro derivatives. The latter can then be reduced to give 1- or 2-alkyloctahydropyrrocolines. Whereas Clemmensen reduction of 1-ketoöctahydropyrrocoline (VI) (29) and the 7-keto derivatives (XIV) (62) proceeds normally, those of 2-keto and 1-methyl-2-keto derivatives yield secondary carbinols; complete reduction is however effected by the Kishner–Wolff method (24, 26). The reduction of the 3-keto derivative has been effected catalytically using copper chromite as catalyst (88).

Clemo and Ramage (29) report the isolation of two forms of octahydropyrrocoline, as picrates, on Clemmensen reduction of VI. Contrary to the balance of published opinion that the three nitrogen valencies in ring systems are coplanar, Clemo *et al.* (30) considered the two forms of the closely related octahydropyridocoline to be *cis–trans* isomers of the decalin type, owing to the non-planarity of the tervalent nitrogen, but Prelog and Seiwerth (78) have recently shown one of the two forms to be identical with bicyclo[0.3.5]aza-1-decane. The derivation of the two forms of octahydropyrrocoline therefore is thus still obscure.

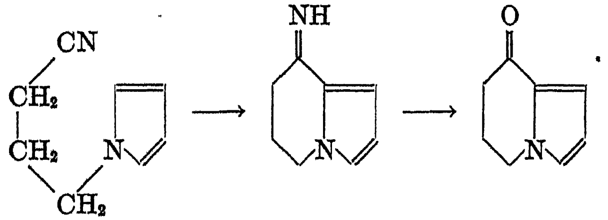
Numerous pyrrocolines have been reduced catalytically to the corresponding octahydro forms, as summarized in Section XII of this review.

Ochiai and coworkers (71) have shown that treatment of 2-methyloctahydropyrrocoline can be converted to the *N*-oxide by treatment with perhydrol.

Hirosawa has reported on the minimal lethal doses for 2-methyl- and 2,3-dimethyl-octahydropyrrocolines, and 1-acetyl-2-methyl-3-aminopyrrocoline which were said to cause convulsions and motor and respiratory paralysis (48).

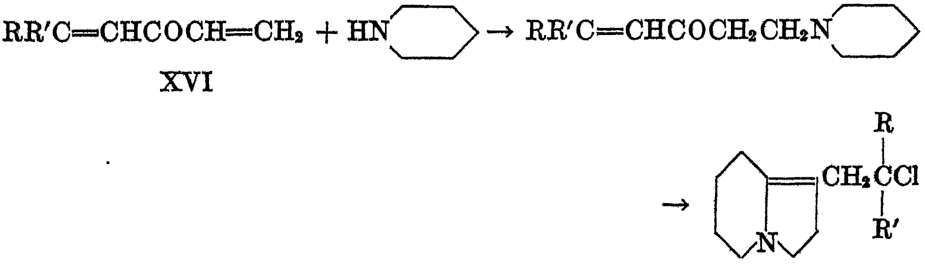
B. Partially reduced pyrrocolines

Selective catalytic hydrogenation of pyrrocolines would appear to be the most suitable method for preparing 5,6,7,8-tetrahydro derivatives (14). 8-Keto-5,6,7,8-tetrahydropyrrocoline is available by ring closure of γ-1-pyrrylbutyronitrile (XIII) to yield an imine hydrochloride (XIV) from which the keto compound (XV) was isolated via the semicarbazone (28).



XIII XIV XV

Nazarov and Zaretskaya (67) have reported the preparation of chloro derivatives (XVII) of hexahydropyrrocolines by addition of piperidine to divinyl ketones (XVI), followed by ring closure by treatment with hydrogen chloride gas.



XVI

XVII

$R = R' = C_2H_5$ and $R = CH_3, R' = C_3H_7$

Other hexahydro derivatives are available by the method of Clemo and Metcalfe (24) involving dehydration of secondary carbinols resulting from the action of Grignard reagents on 1- and 2-ketoöctahydropyrrocolines.

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